

Anatomical and Functional Magnetic Resonance Imaging in Small Animal Models

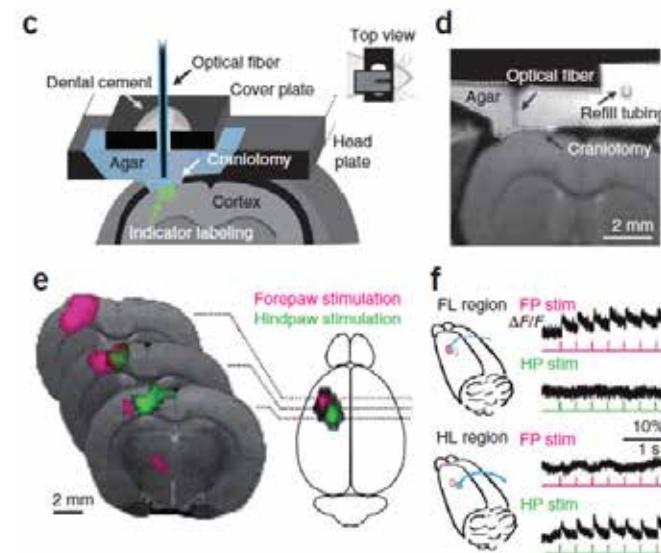
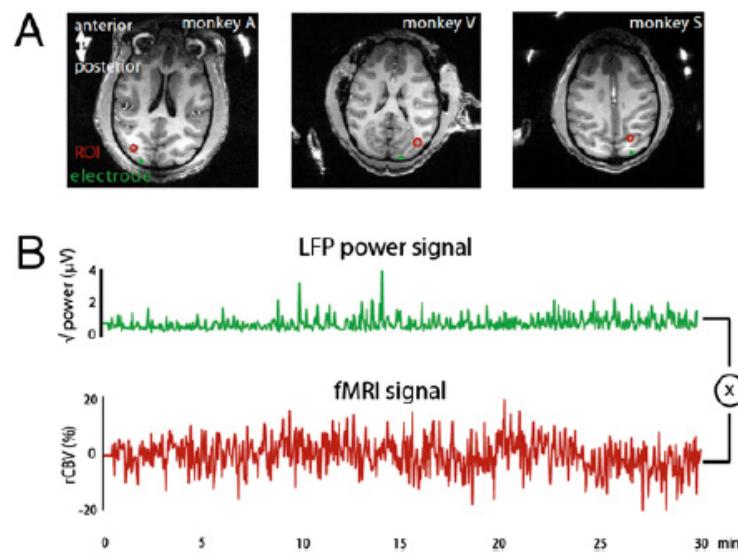
Afonso C. Silva, Ph.D.

Cerebral Microcirculation Unit
Laboratory of Functional and Molecular Imaging
NINDS - NIH



Advantages of Animal Models

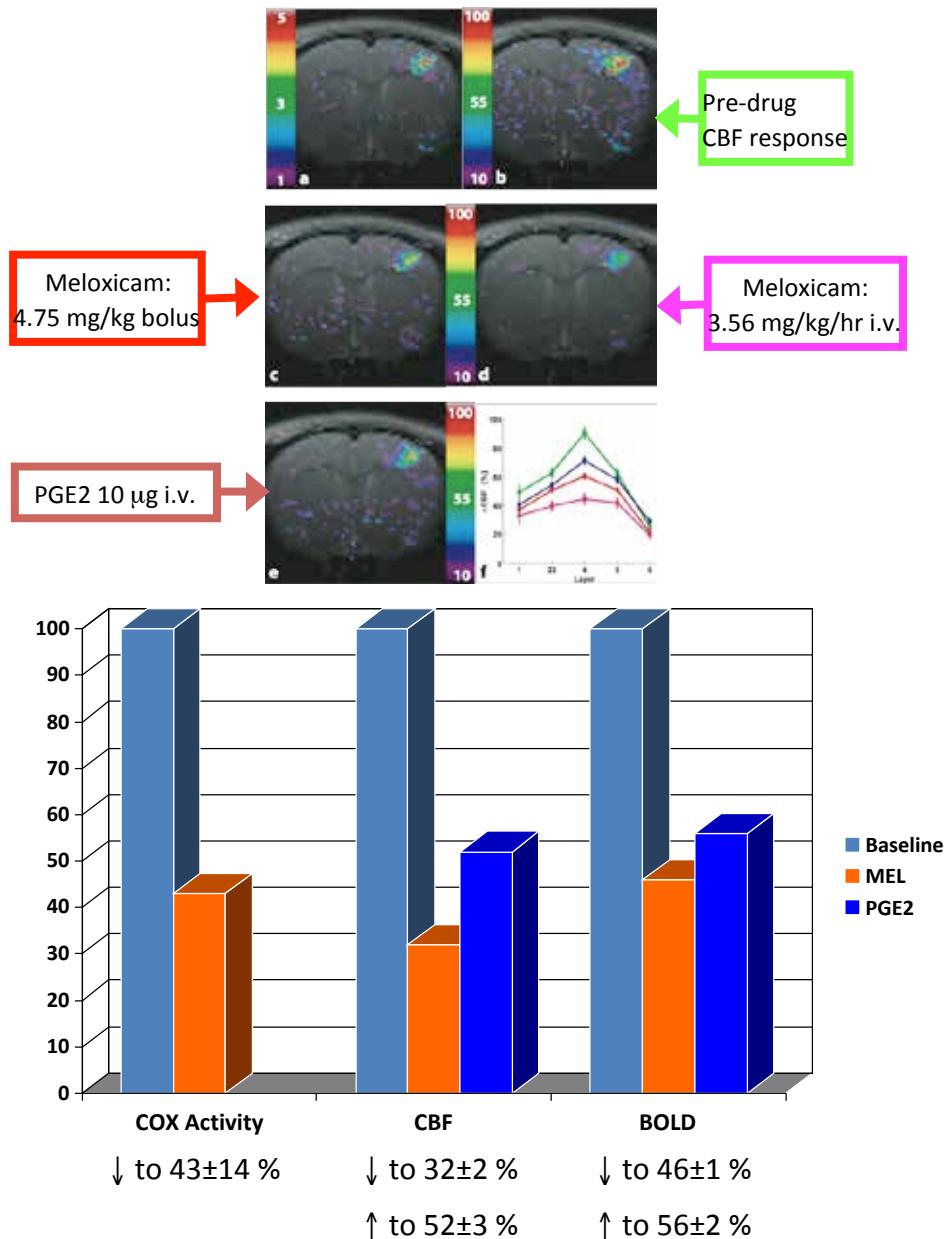
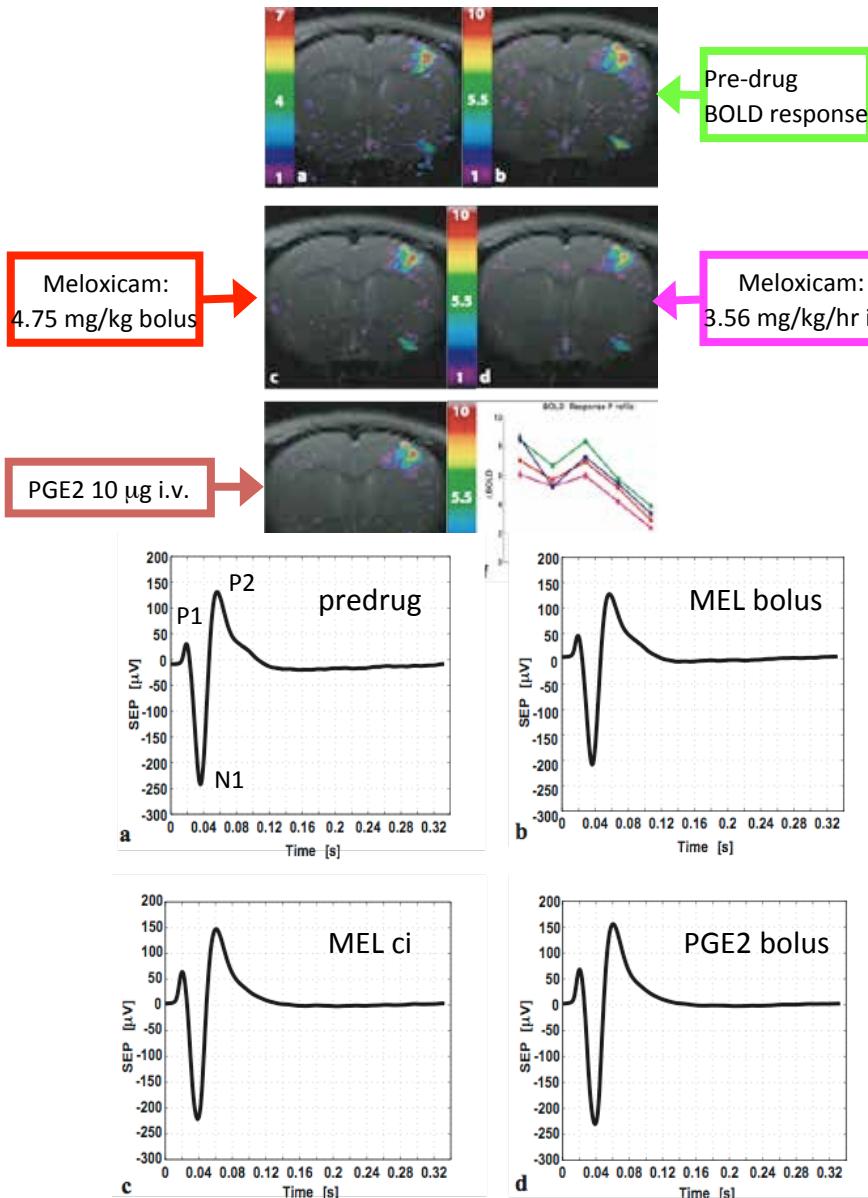
- Comprehensive, multi-modal investigations
 - fMRI + Electrophysiology
 - fMRI + Optical Imaging
 - Pharmacological Manipulations
 - Genetics, etc.



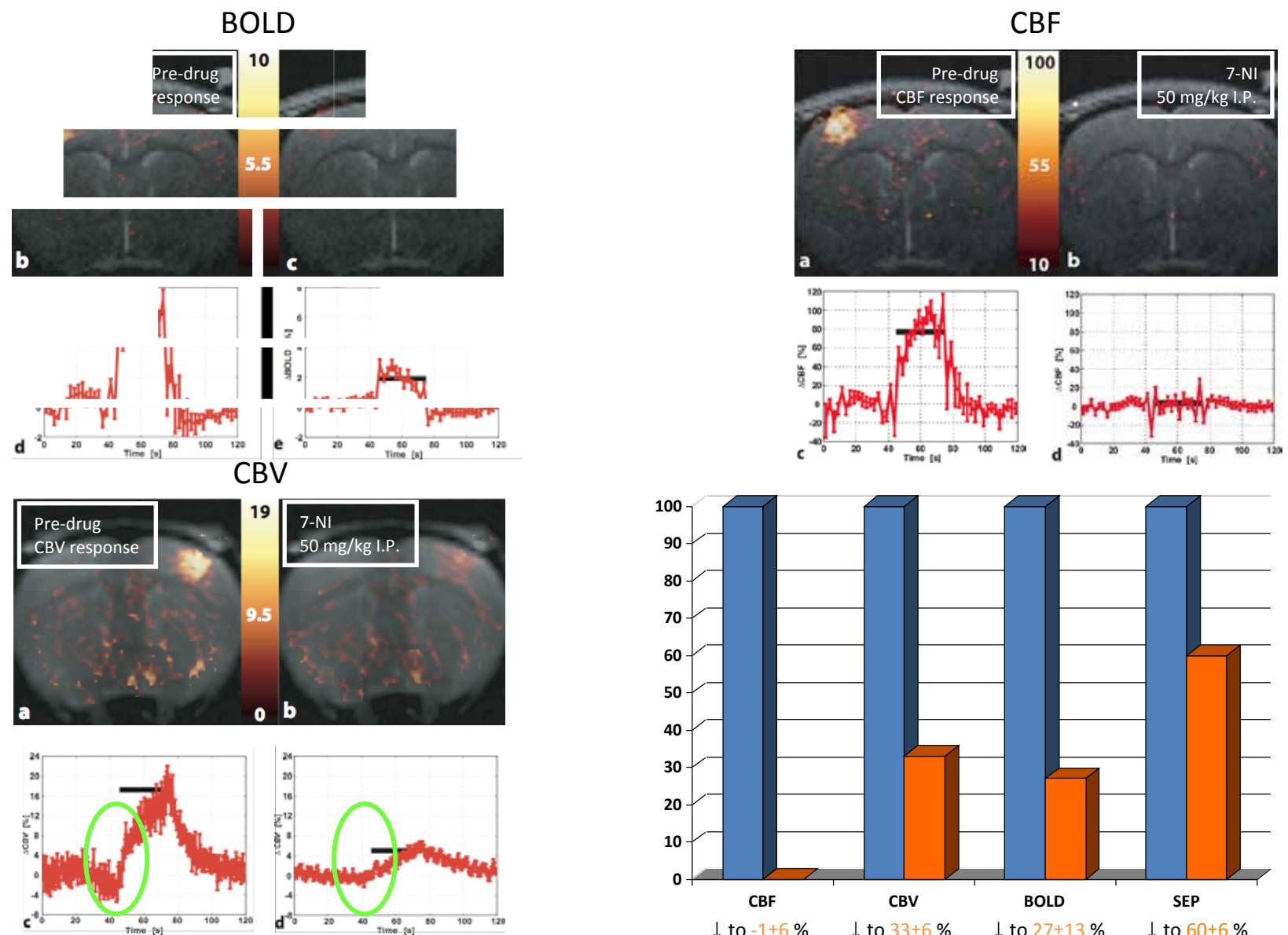
Schölvicck et al. Proc Natl Acad Sci USA. 2010;107(22):10238-43

Schultz et al. Nat Methods. 2012;9(6):597-602

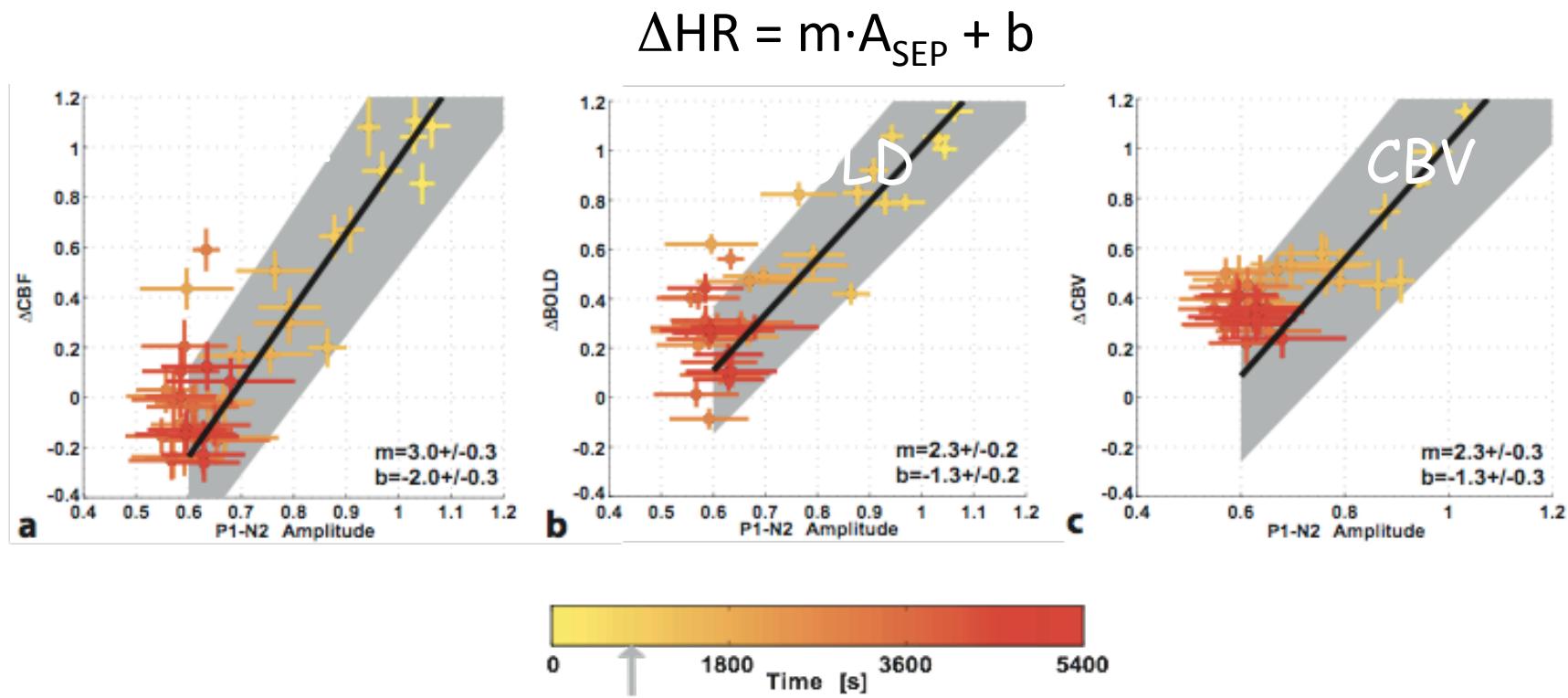
Pharmacological Inhibition of COX-2 Uncouples Hemodynamics from Neural Activity



Pharmacological Inhibition of Nitric Oxide Uncouples BOLD from CBF

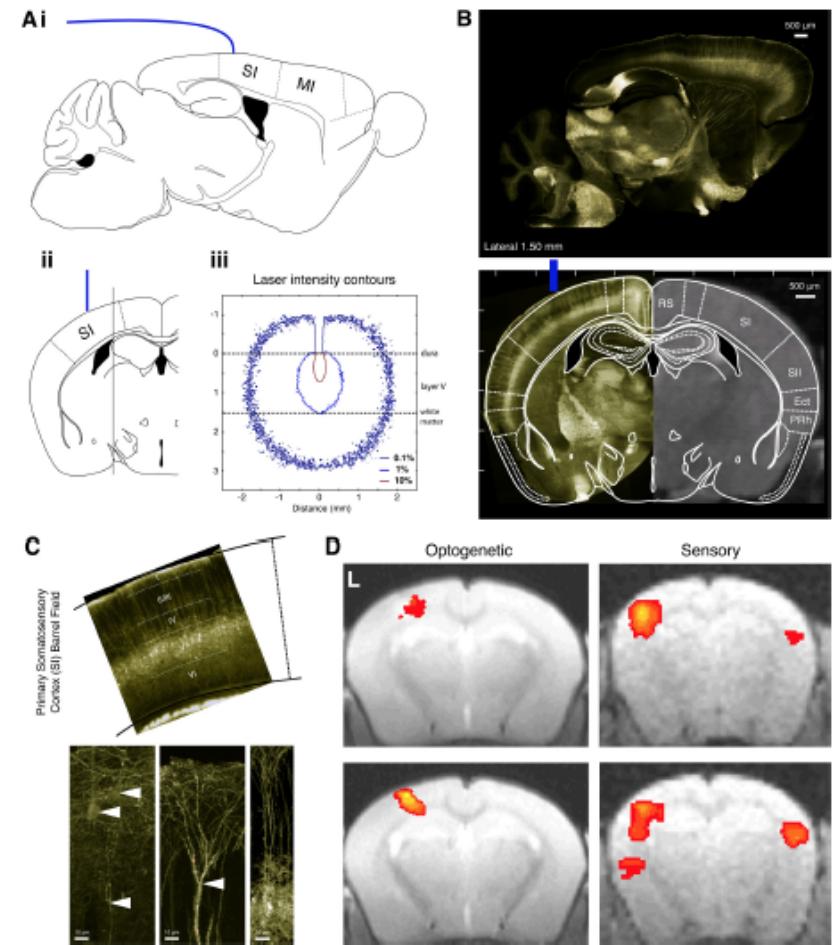
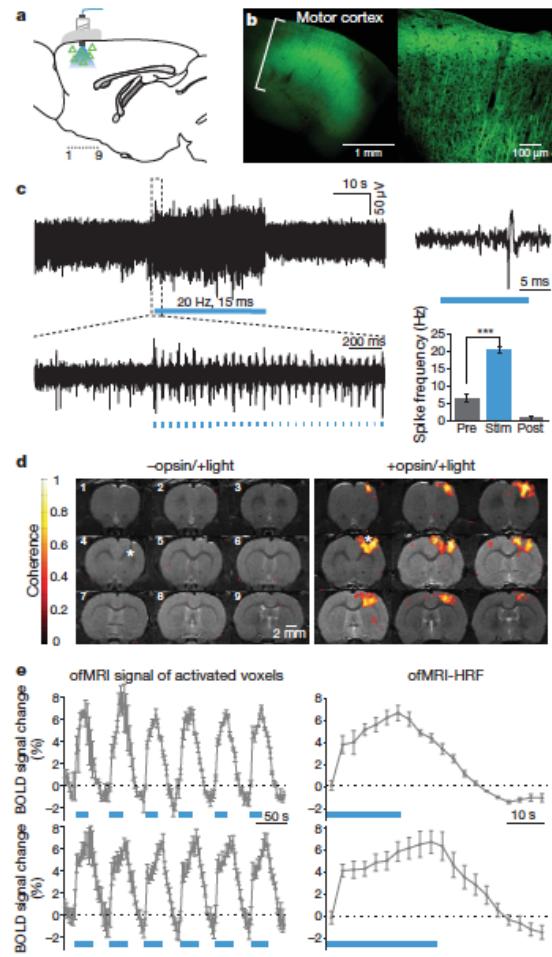


Neurovascular Uncoupling Upon NO Inhibition



- $m > 0$ = larger attenuation of HR w.r.t. SEP
- $b < 0$ = minimum SEP amplitude necessary to elicit HR, i.e., neuronal activity can be sustained in absence of HR

Genetic Manipulations: Optogenetics

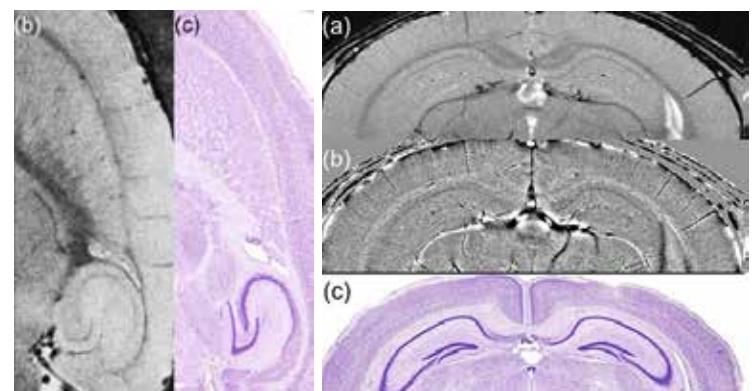


Lee et al. Nature. 2010 Jun 10;465(7299):788-92

Kahn et al., J Neurosci. 2011 Oct 19;31(42)

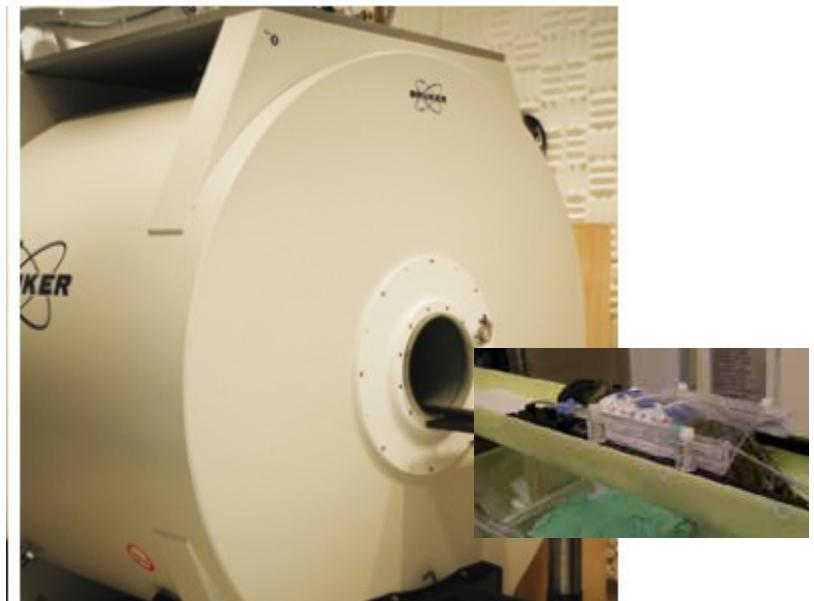
Advantages of Animal Models

- Technical
 - Ultra-High Field Magnets
 - up to 21T vertical
 - up to 17.6T horizontal
 - Stronger Gradients
 - Up to 1000 mT/m in 12 cm ID
 - Small FOV due to smaller brain size
 - Improved spatial resolution
 - Improved SNR with specialized RF coils

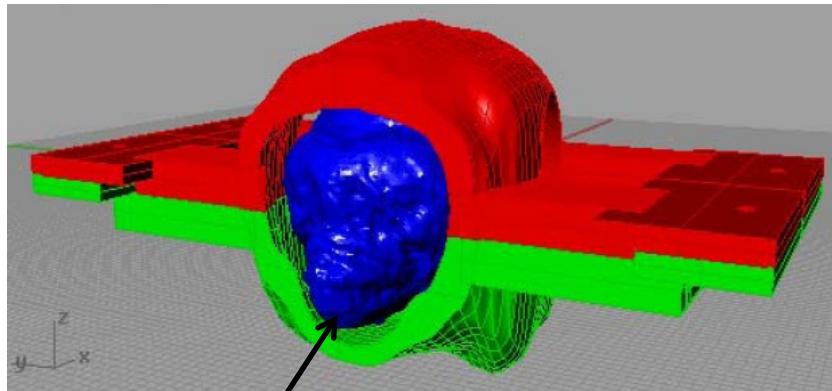


How to Do MRI/fMRI in Small Animals

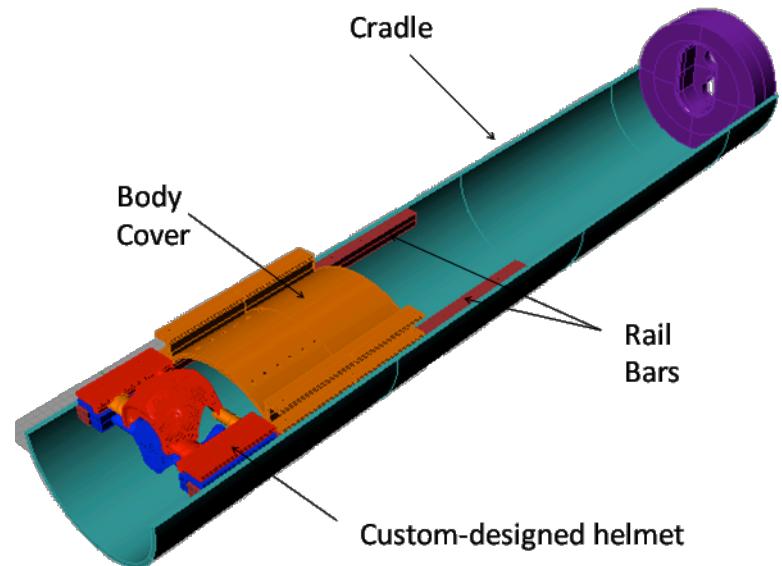
- Two types of setup
 - Anesthetized Animals
 - Isoflurane (anatomic studies)
 - Chloralose (functional studies)
 - Propofol + Fentanyl (functional studies)
 - Awake
 - Anatomical or functional Studies
- Extensive Physiological Monitoring
 - Temperature
 - Blood Pressure and Heart Rate
 - Pulse oximetry
 - ETCO₂



Anatomical and Functional MRI in Conscious, Awake Marmosets

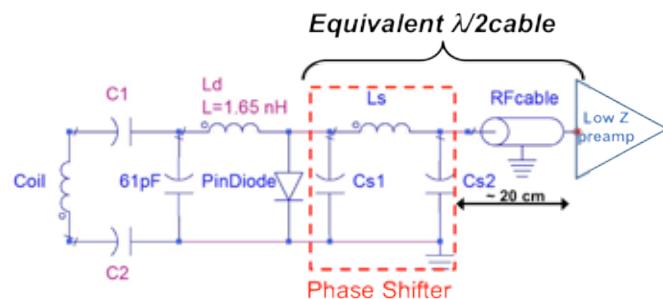


Individual
Helmet

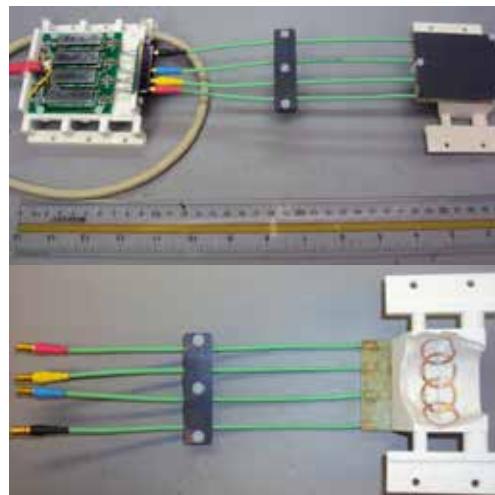


State-of-the-Art Neuroimaging Techniques

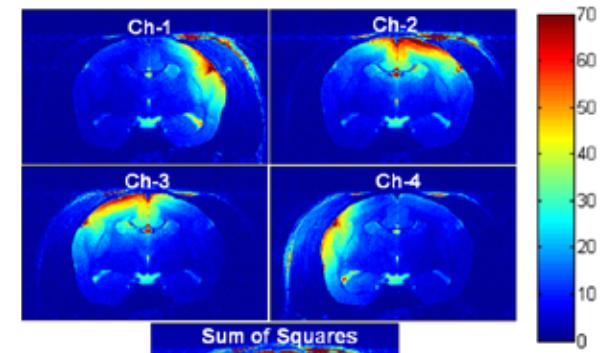
- Embedded RF receiver arrays



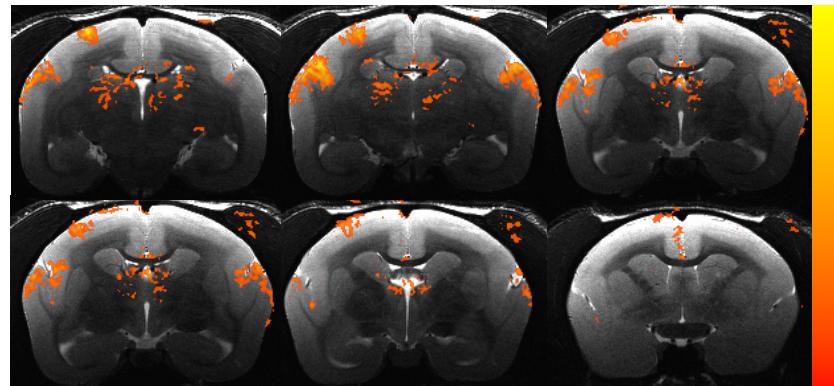
Circuit Diagram



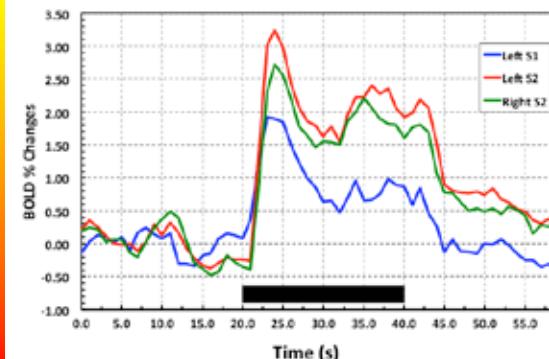
Embedded helmet array and preamps



In vivo SNR Maps

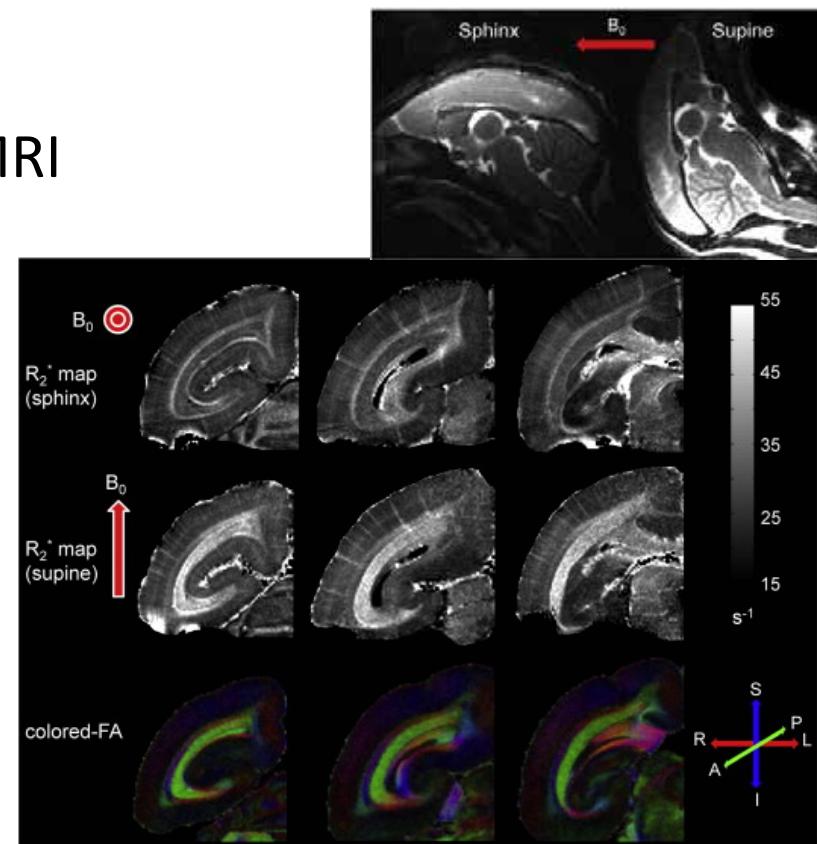
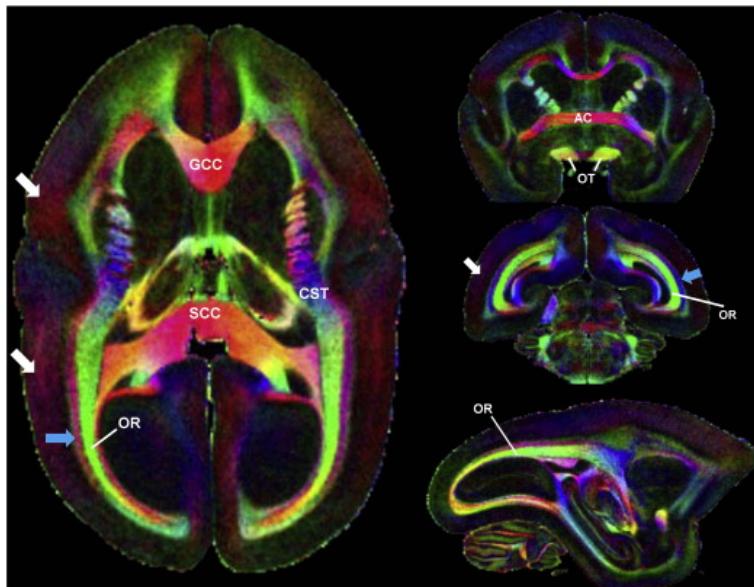


fMRI in Conscious, Awake Marmosets
 $250 \times 250 \times 1000 \mu\text{m}^3$

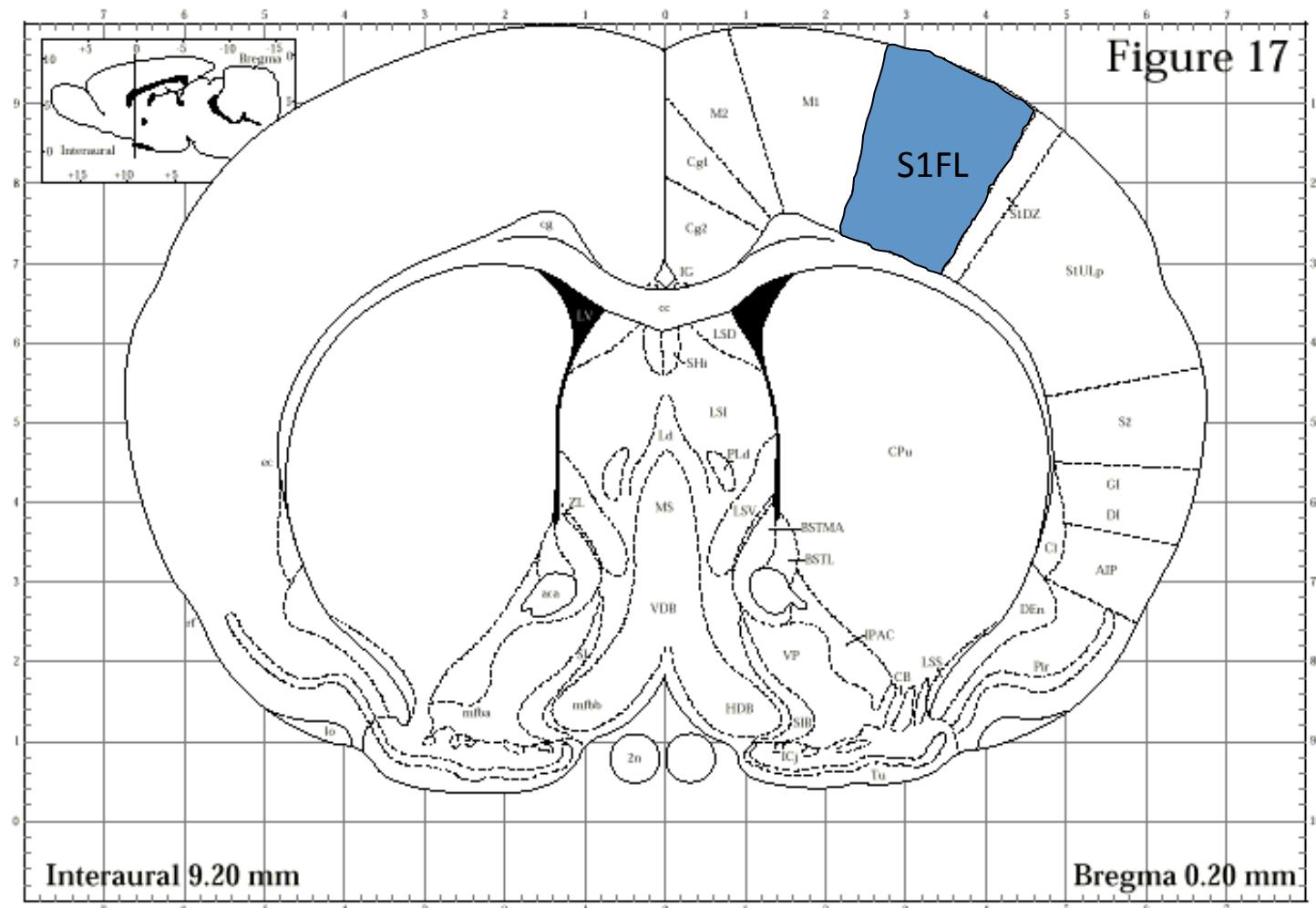


State-of-the-Art Neuroimaging Techniques

- High Resolution Anatomical MRI

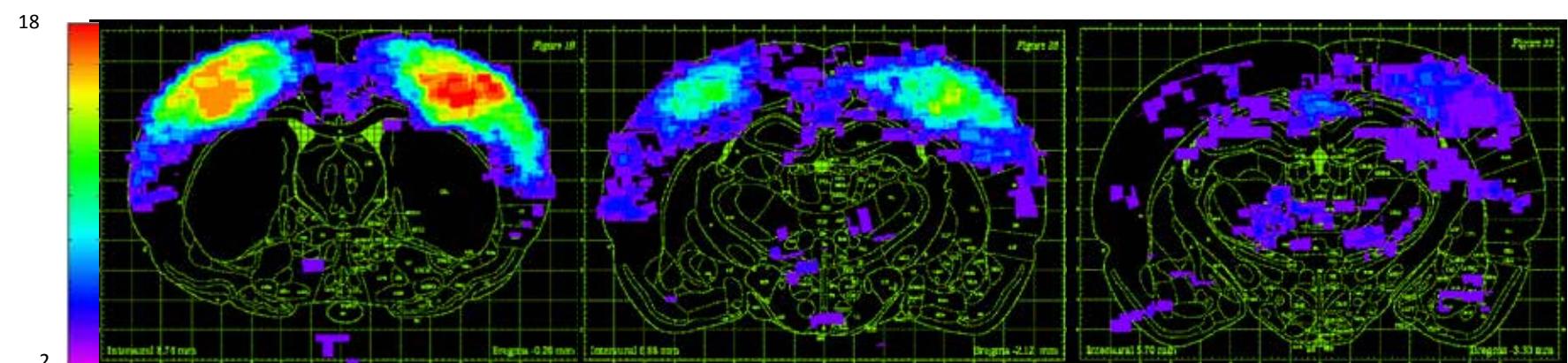
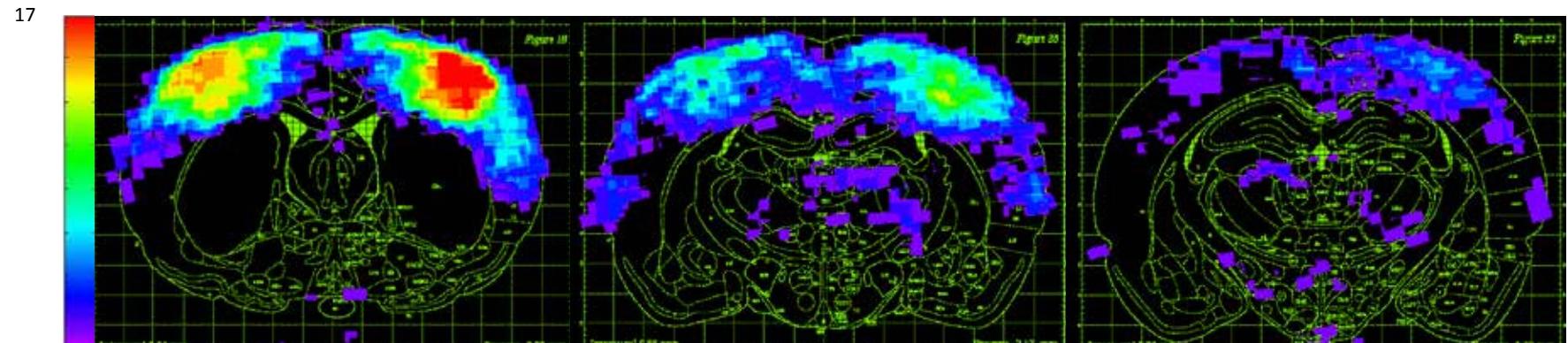


How to Stimulate Animals: Somatosensory Stimulation in Rat

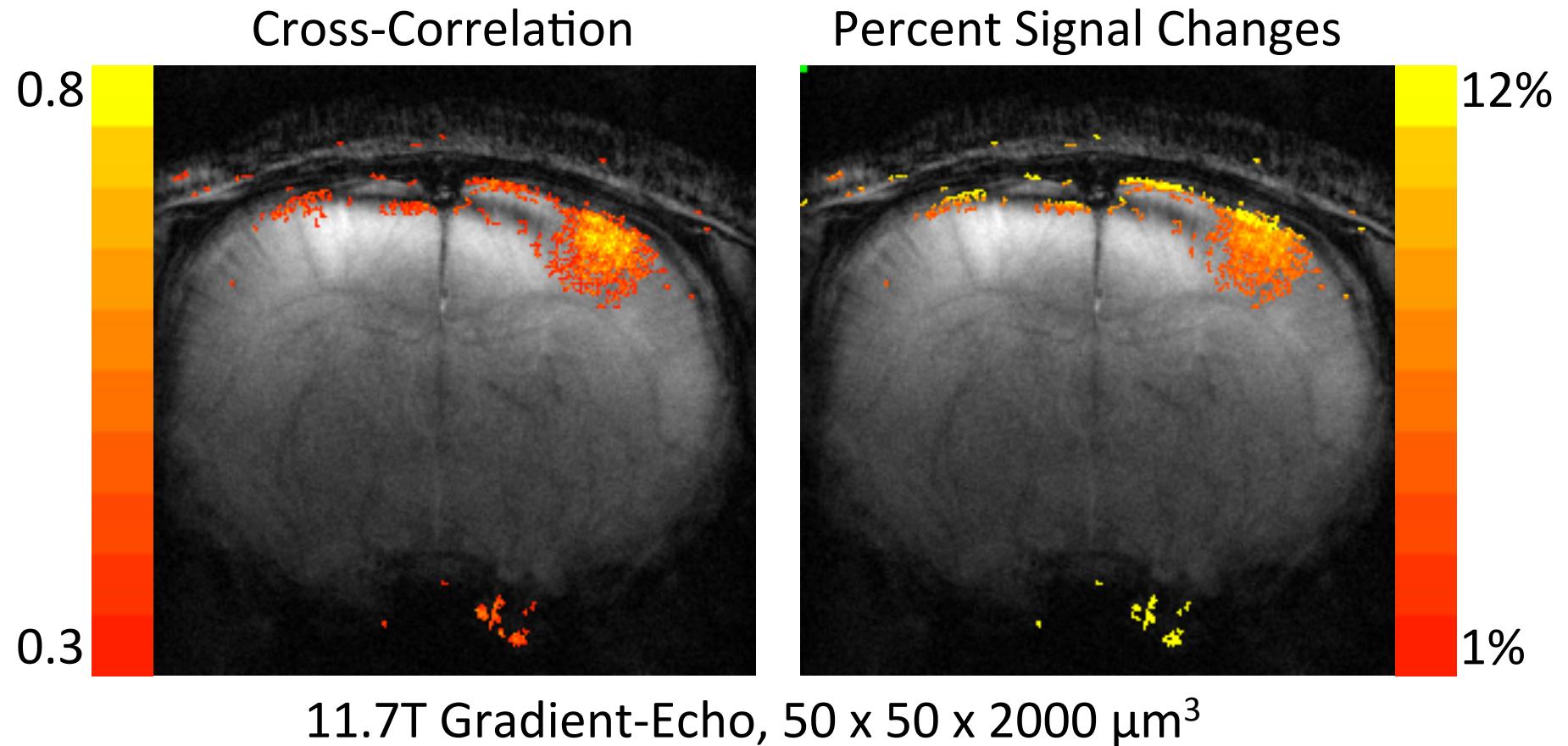


Atlas: "The Rat Brain in Stereotaxic Coordinates", Paxinos & Watson, 1998

Reproducibility: BOLD and CBV Incidence Maps at 11.7T

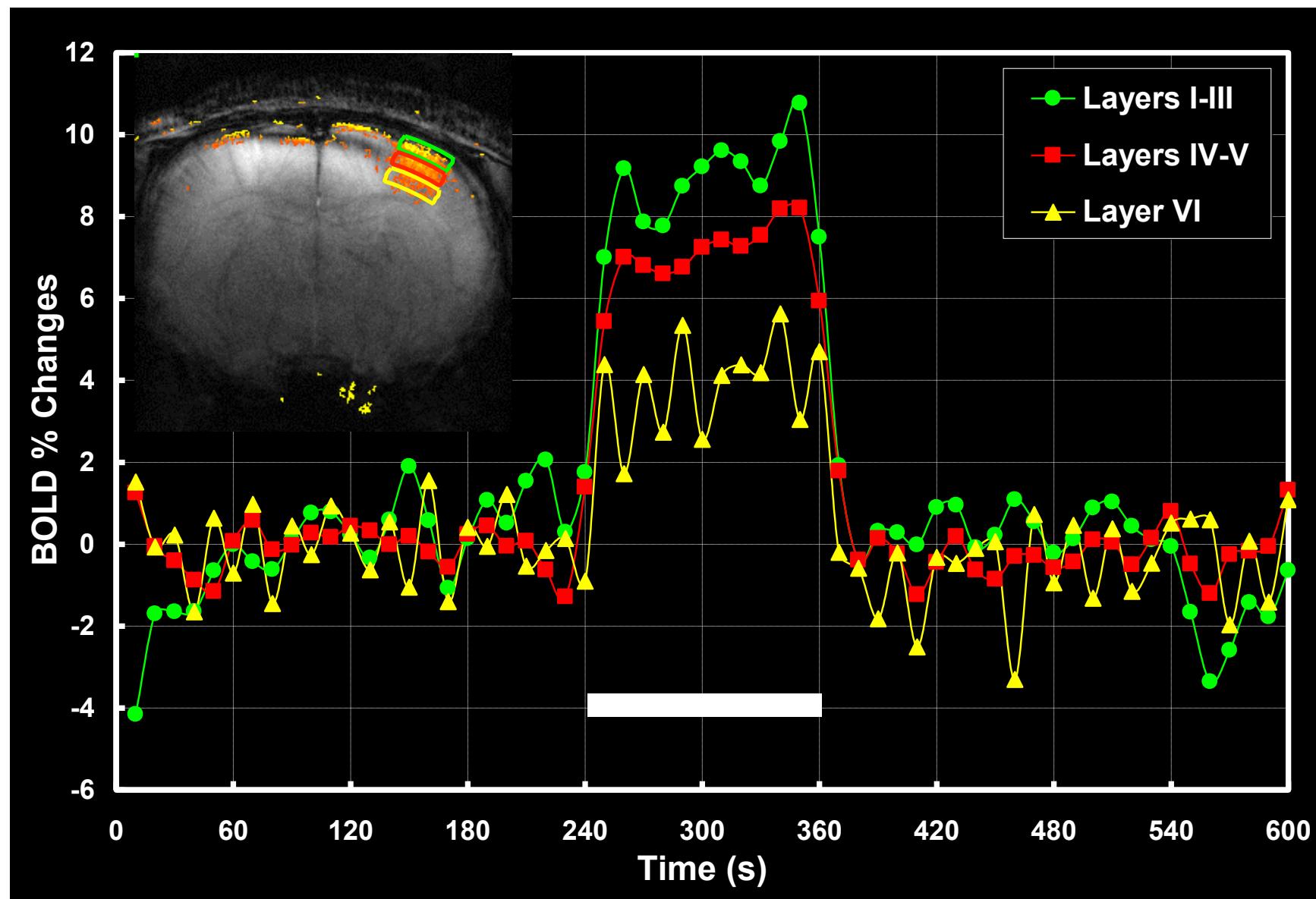


Spatial Resolution: BOLD Functional Maps



Silva and Koretsky PNAS 99: 15182-15187 (2002)

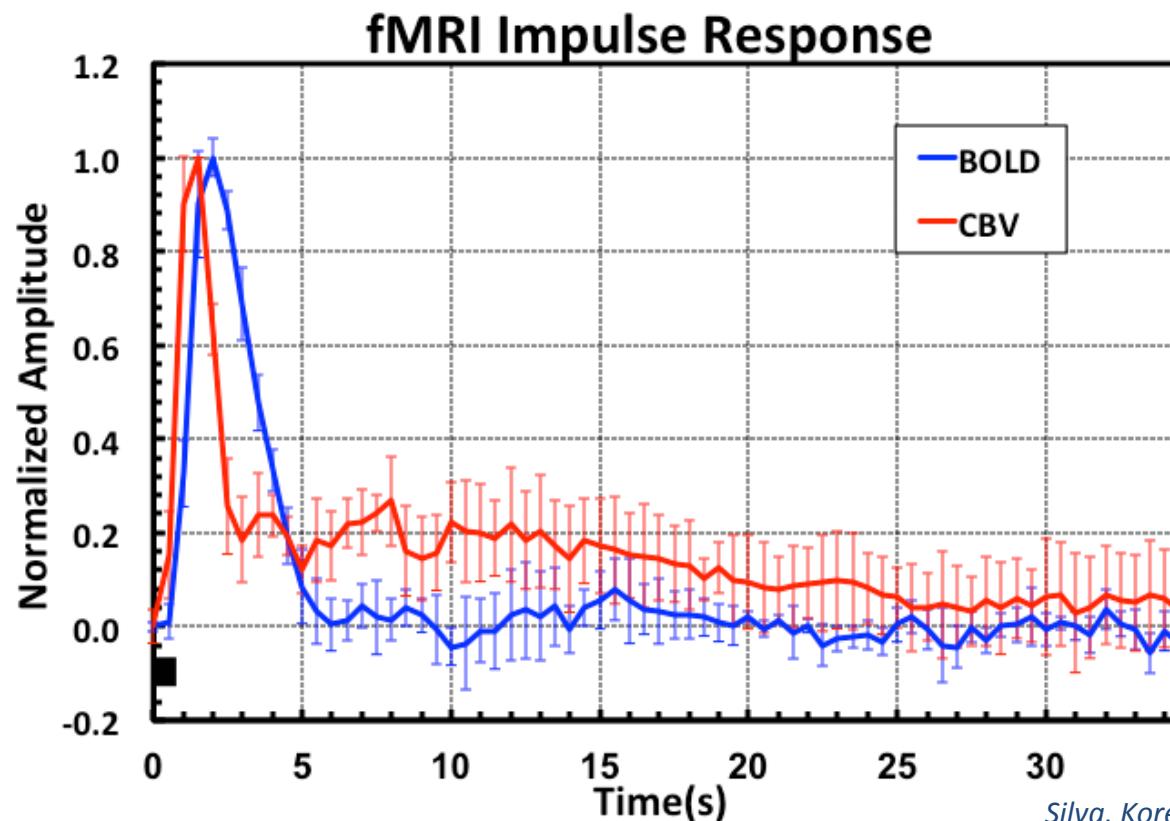
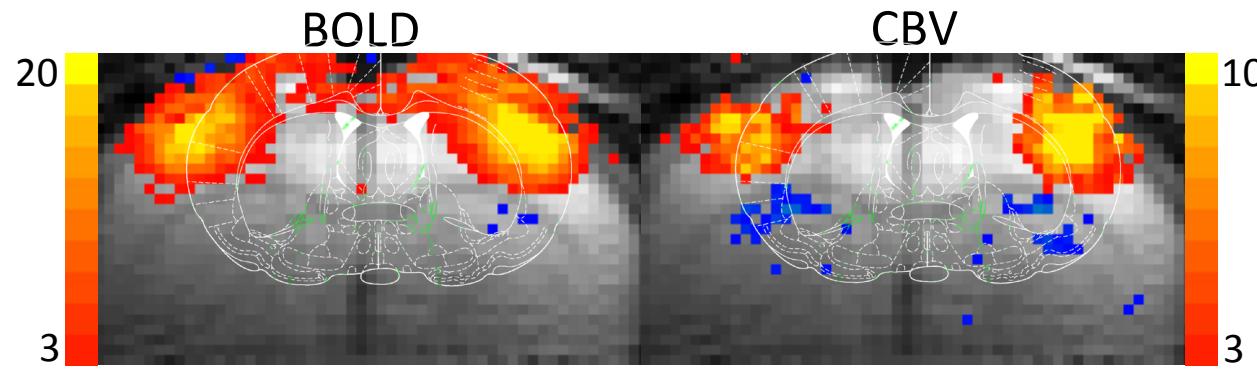
Laminar Specificity of BOLD Signal Changes



Laminar Specificity of BOLD % Changes

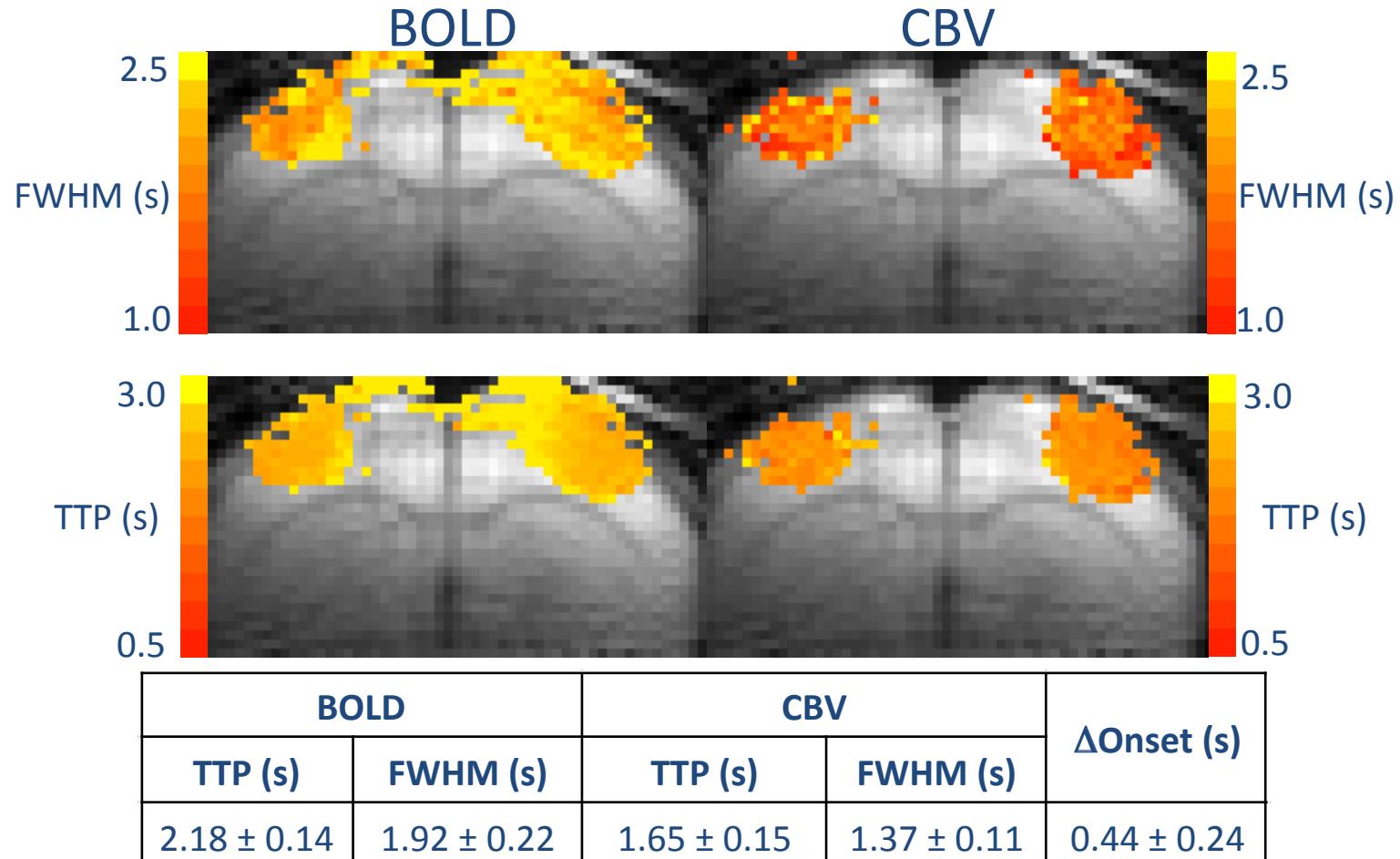
	Layers I-III	Layers IV-V	Layer VI
50 × 50 μm^2 120 s stimulus	8.4 ± 3.6	5.7 ± 1.9	3.8 ± 1.1
200 × 200 μm^2 30 s stimulus	8.2 ± 4.6	5.4 ± 2.2	3.1 ± 1.0
200 × 200 μm^2 4 s stimulus	4.2 ± 1.8	2.9 ± 1.2	1.6 ± 0.4

BOLD and CBV Impulse Responses



- α -chloralose anesthetized rat
- Electrical stimulation of the forepaw
- Stimulation parameters optimized by laser-Doppler flowmetry:
 - 2.0 mA; 3 Hz; 0.3 ms

Parametric Maps: Time-to-Peak (TTP) & Full-Width at Half-Maximum (FWHM)

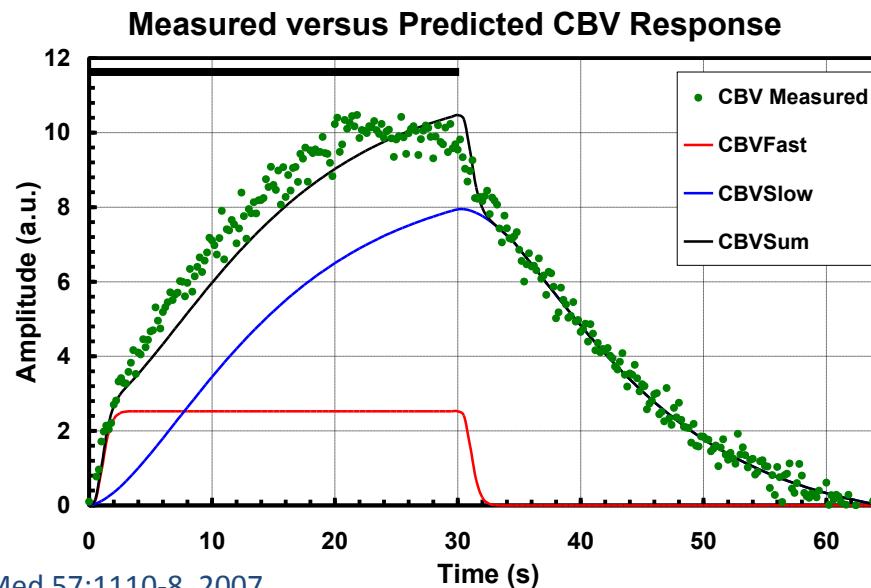
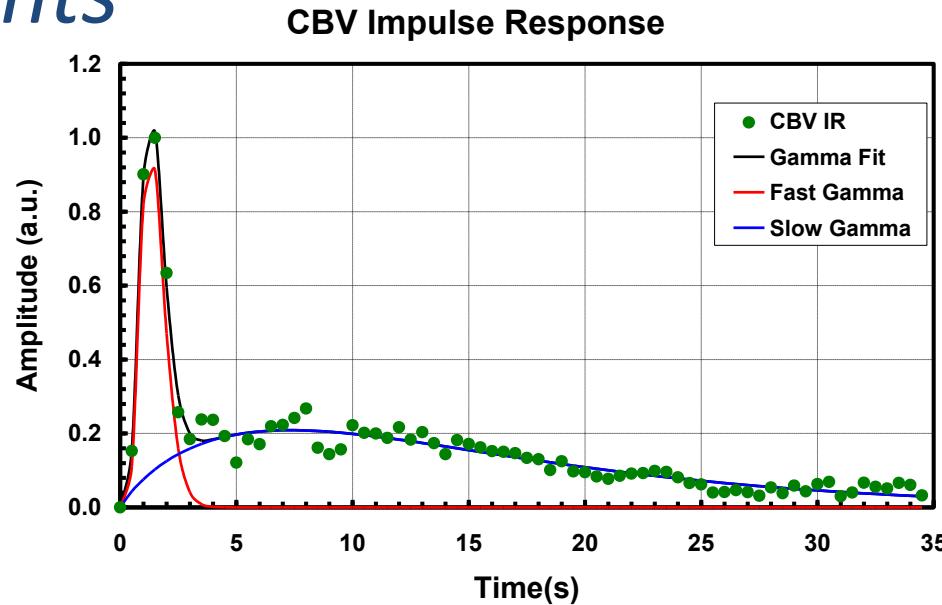


Compare to $TTP = 4.51 \pm 0.52$ s and $FWHM = 4.04 \pm 0.42$ s

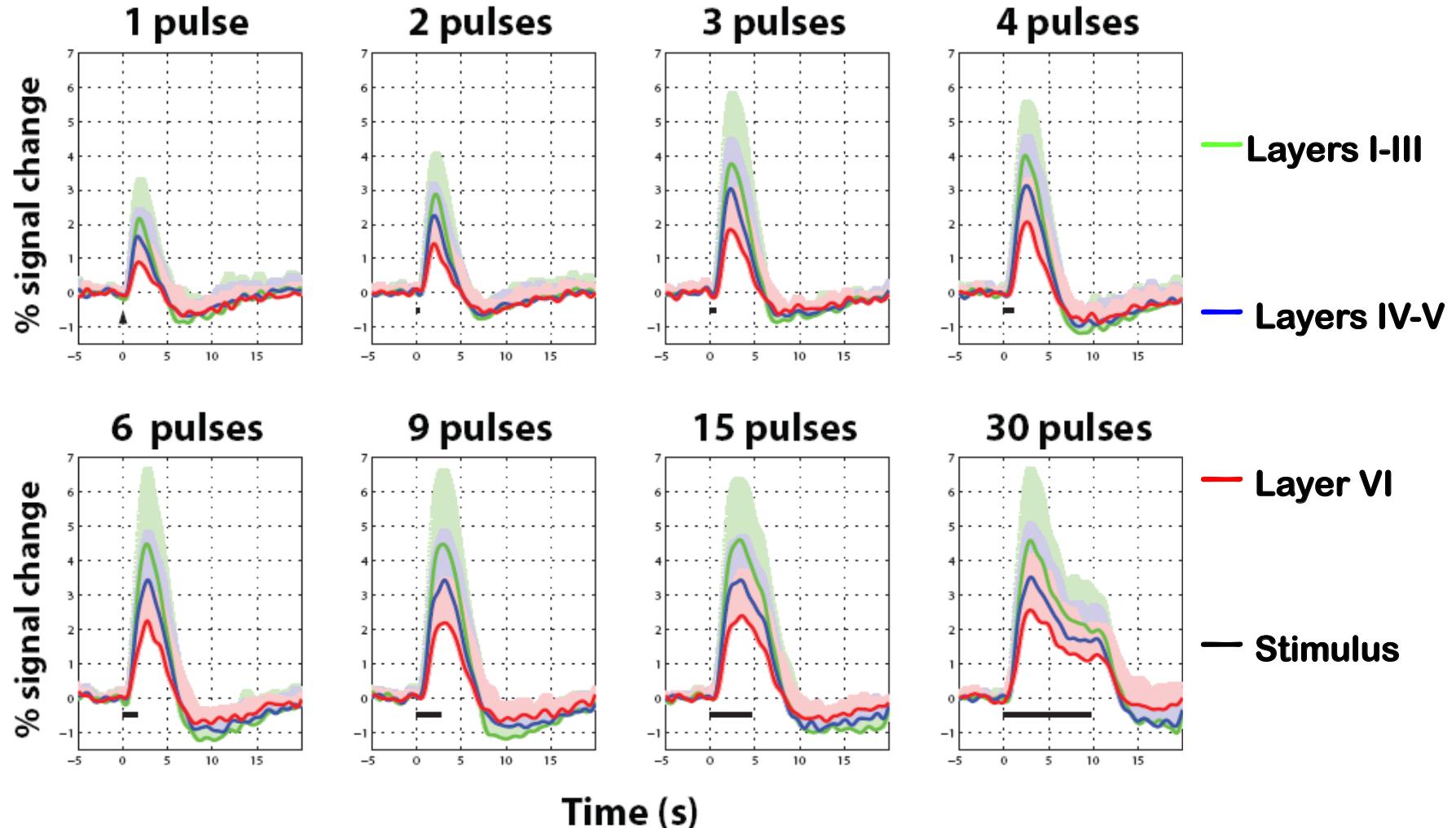
in humans (*de Zwart et al, Neuroimage 24:667-677 (2005)*)

Silva, Koretsky, Duyn, Magn Reson Med 57:1110-8, 2007

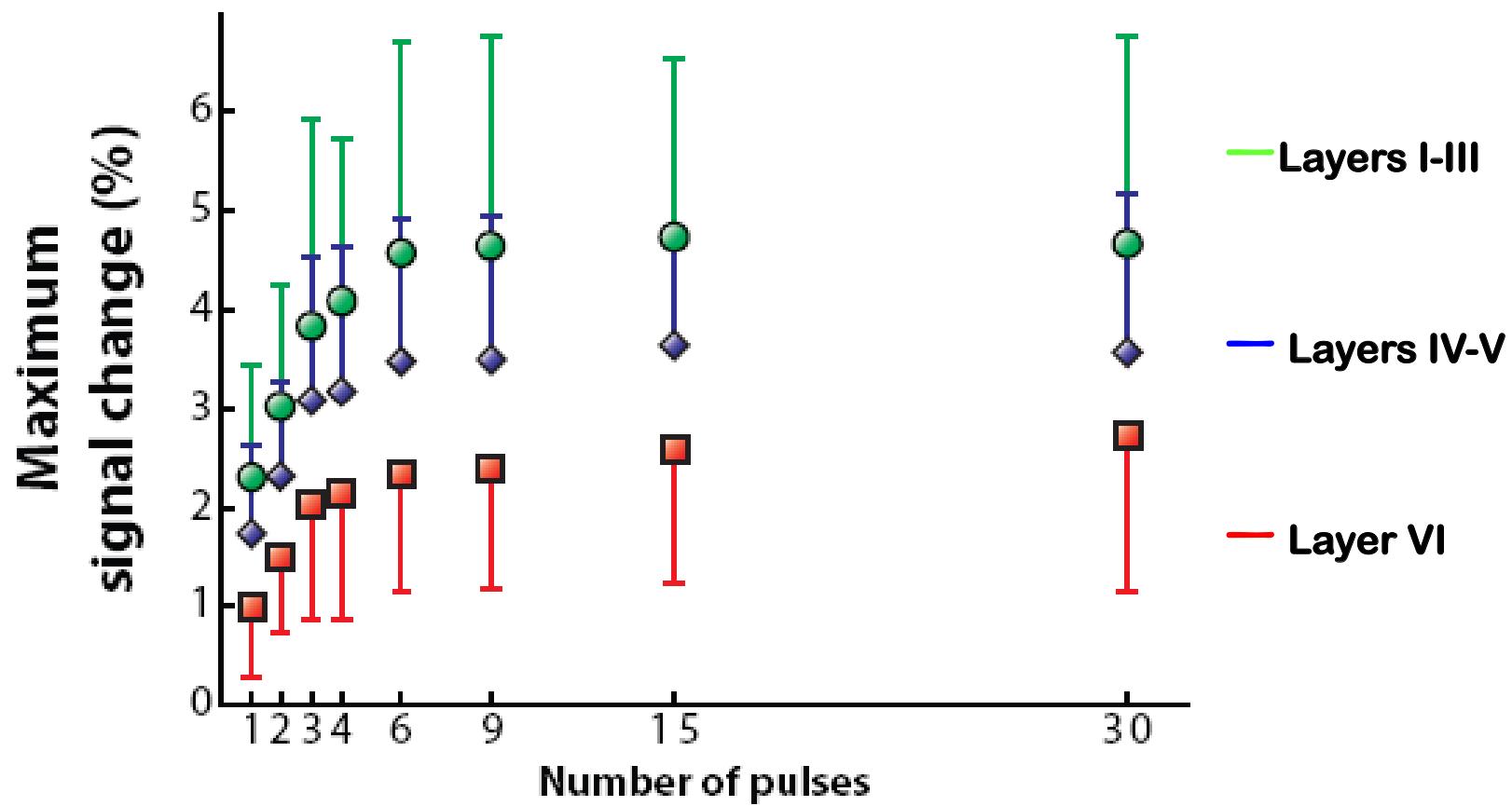
CBV Impulse Response Has Fast and Slow Components



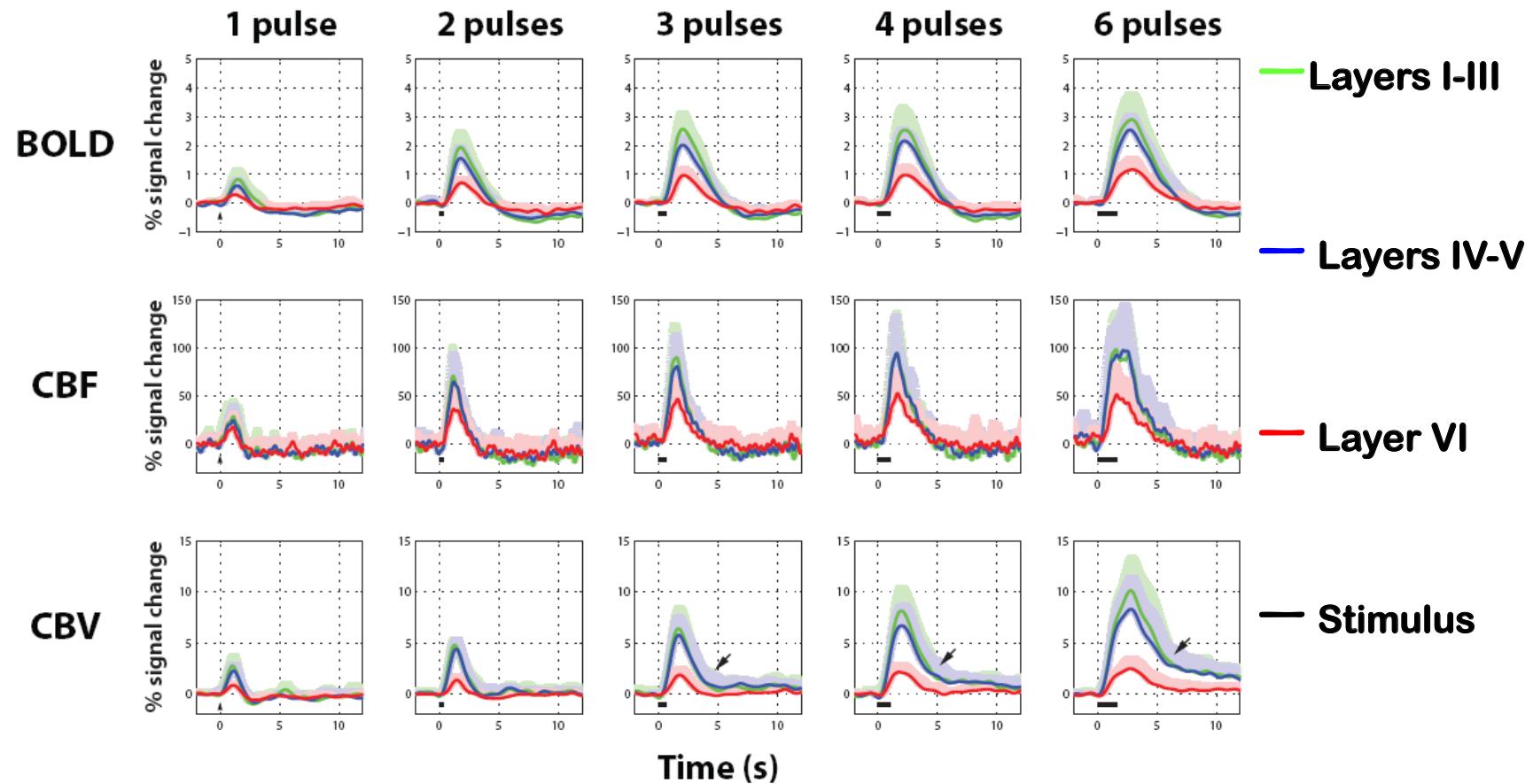
Variation of HDR with Stimulus Duration



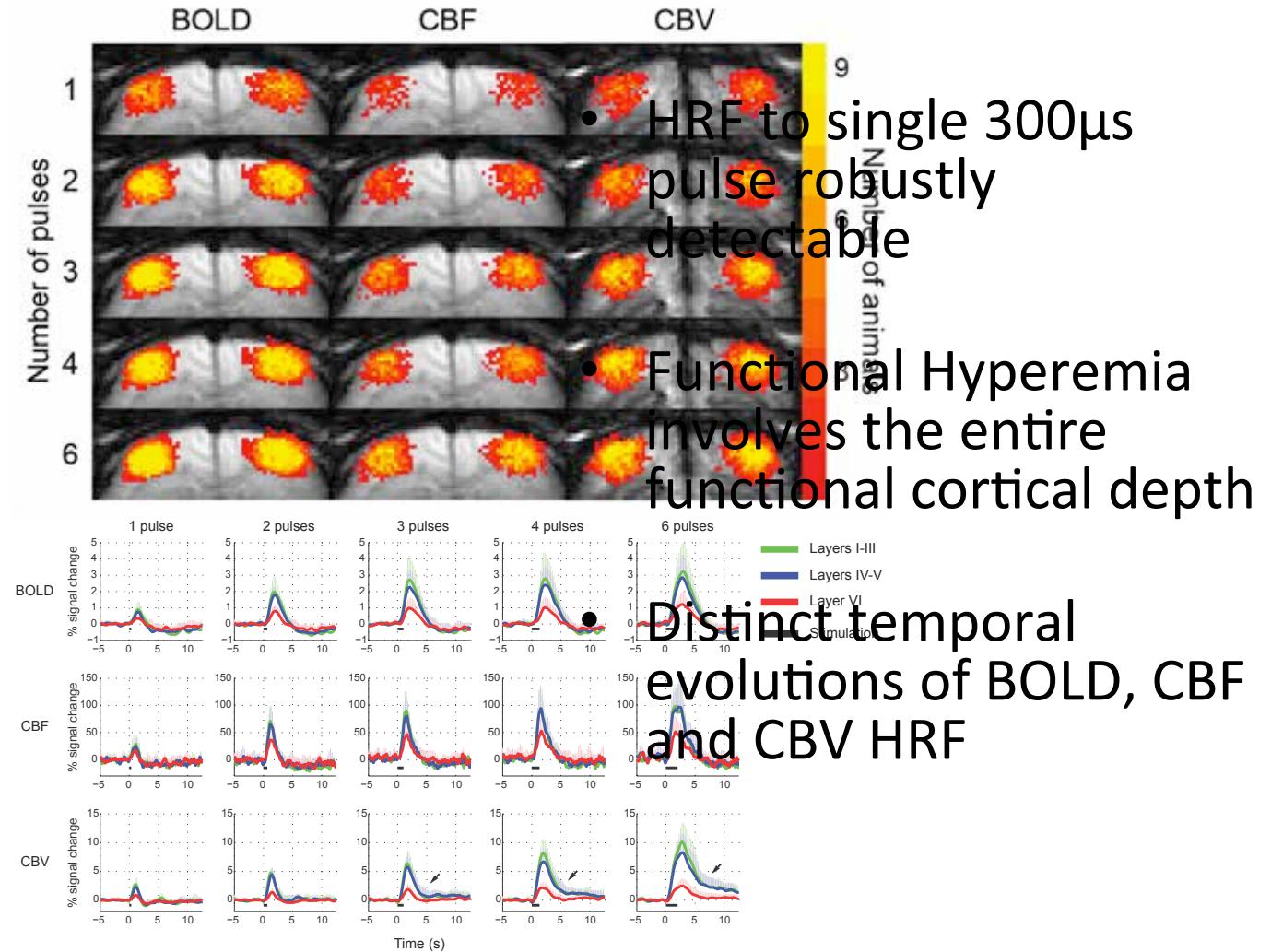
Variation of the Peak Intensity with Stimulus Duration



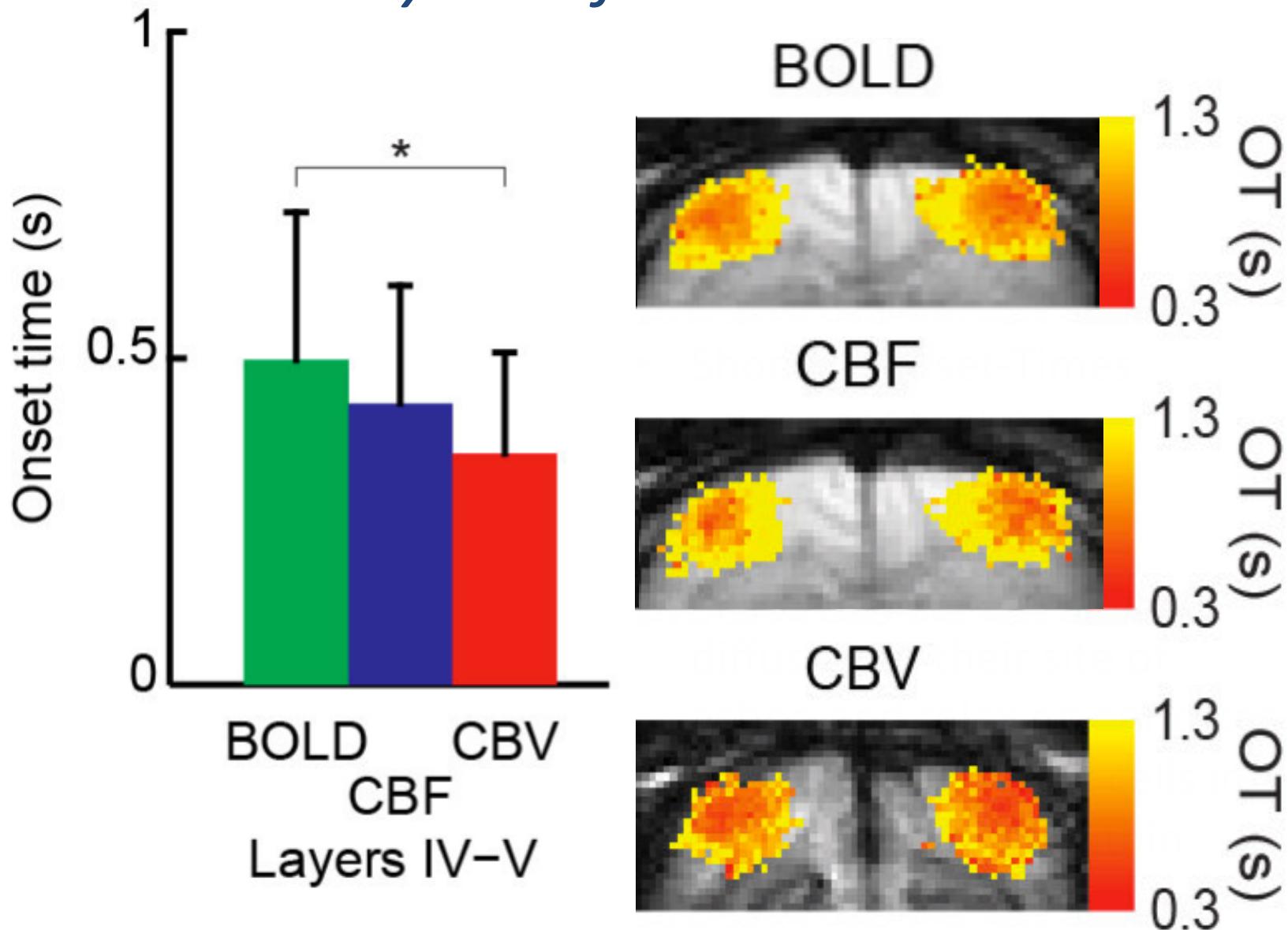
BOLD, CBF and CBV Have Distinct Temporal Characteristics



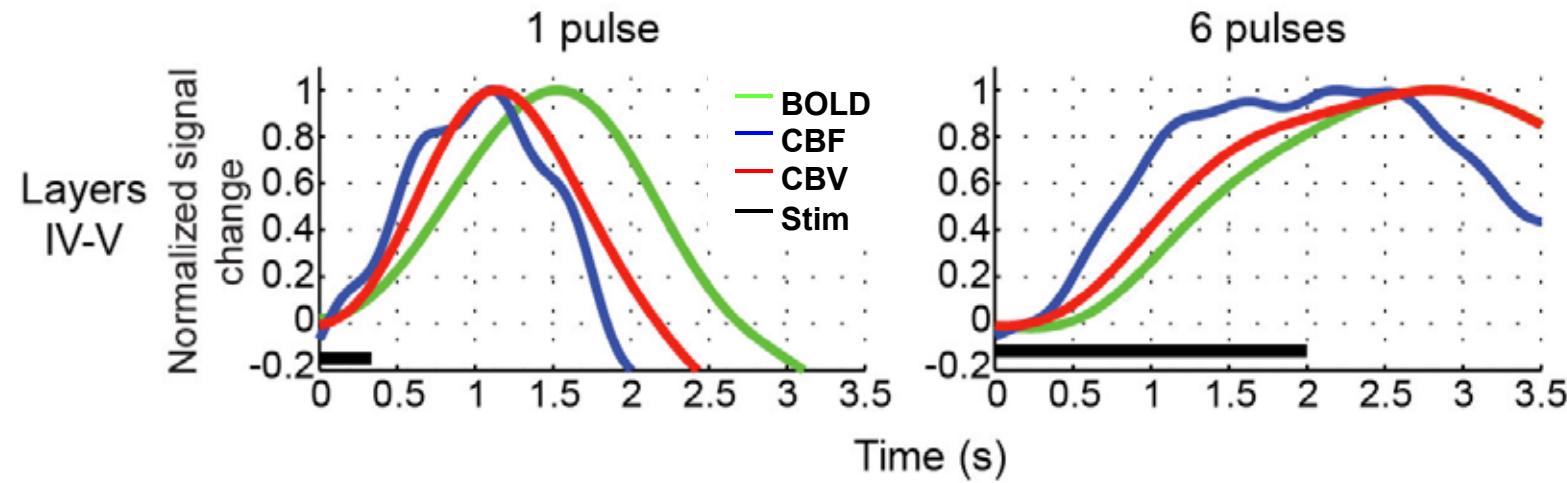
Robust fMRI Responses to Ultrashort Stimuli



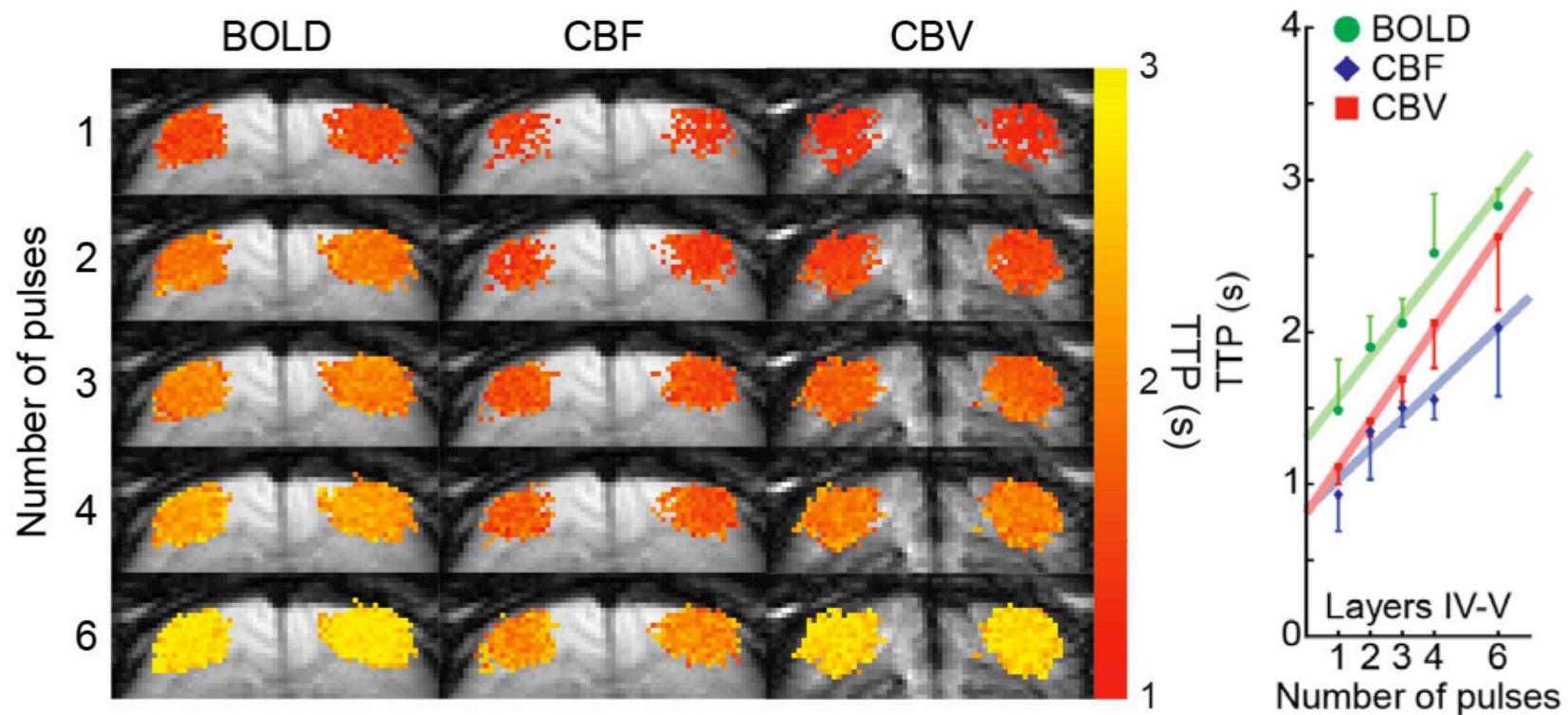
Remarkably Fast fMRI Onset Times



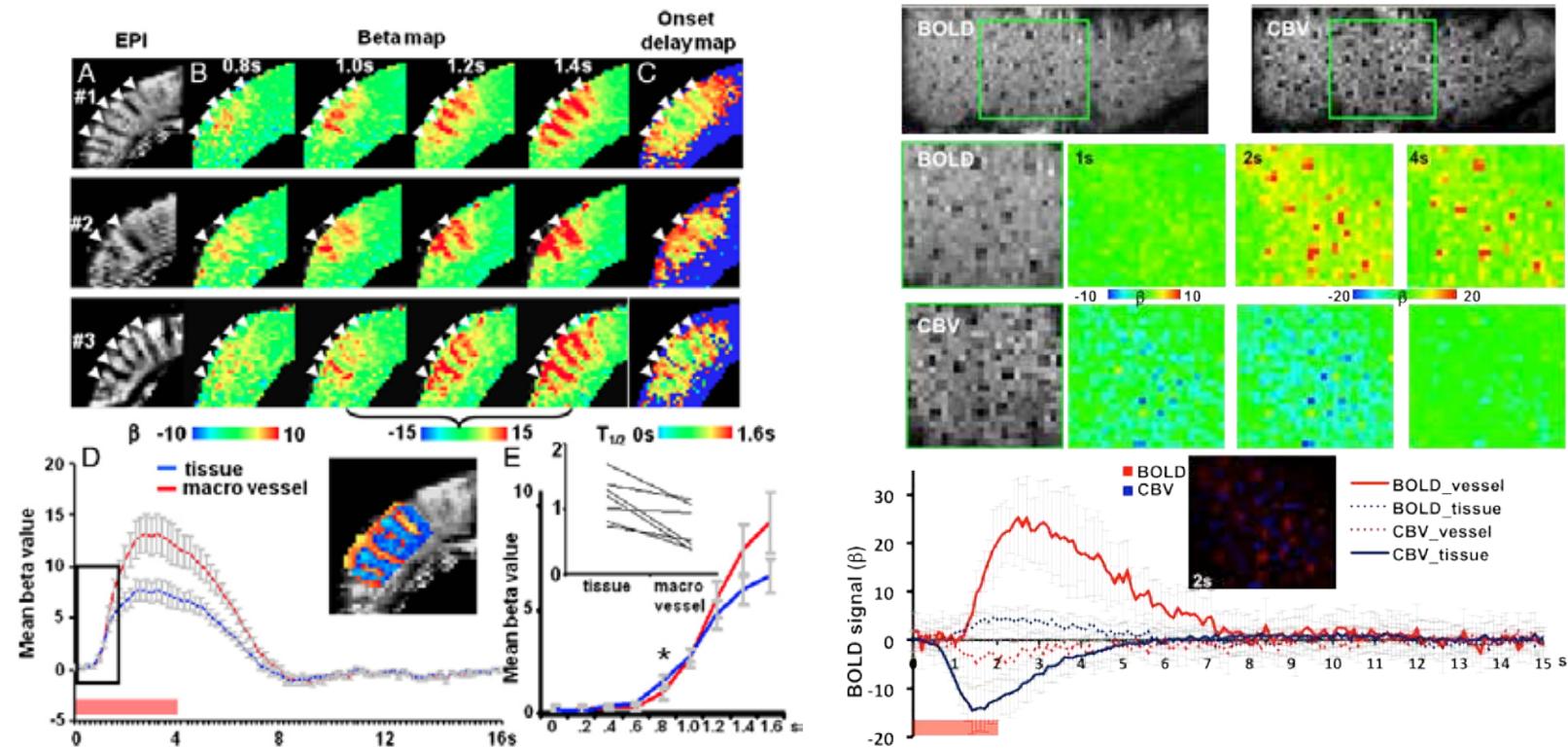
Distinct Temporal Evolution of CBV HRF



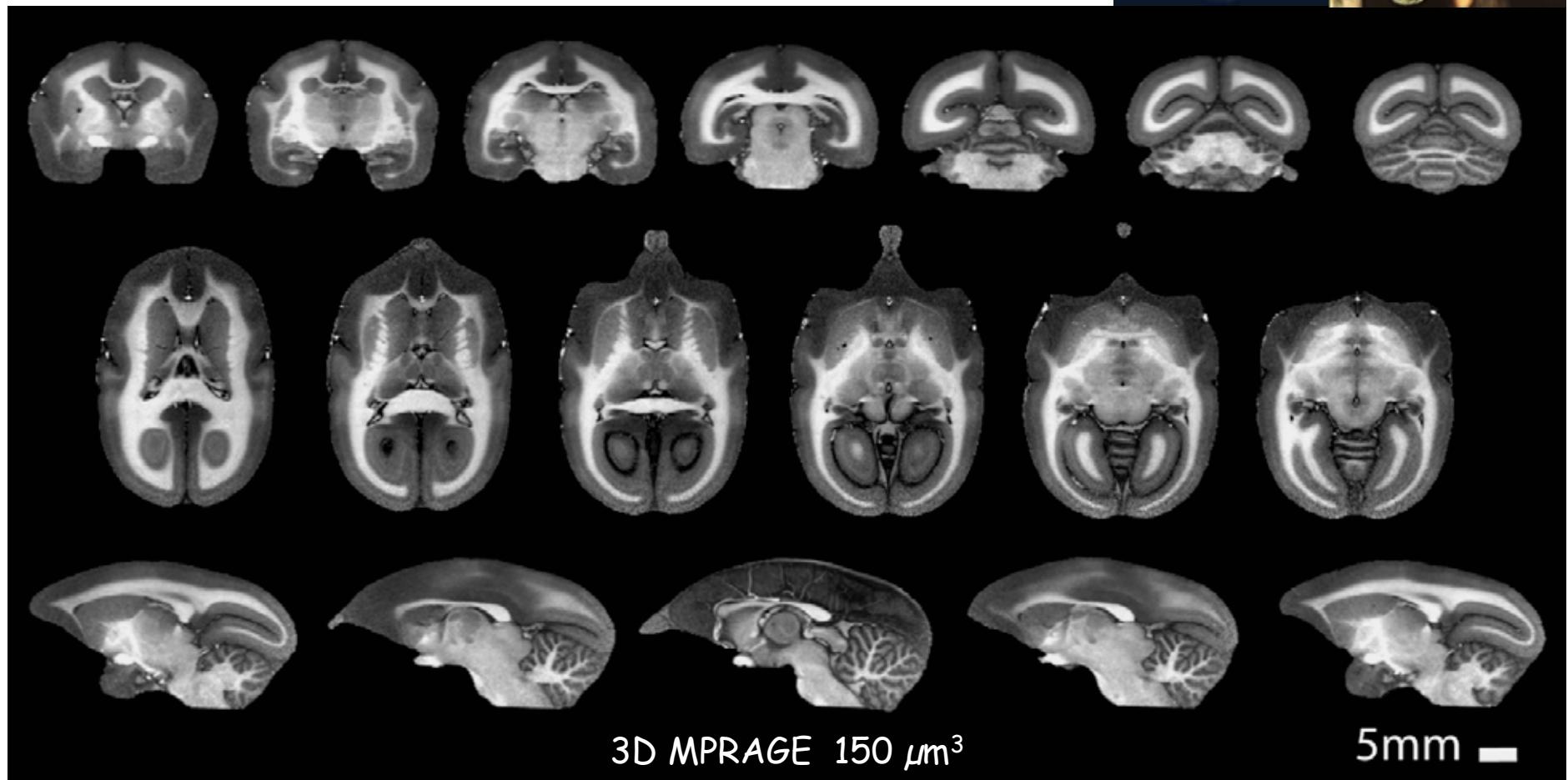
Distinct Temporal Evolution of CBV HRF



High Resolution fMRI Shows Early Activation of Capillary Network



Anatomical MRI of the Marmoset Brain

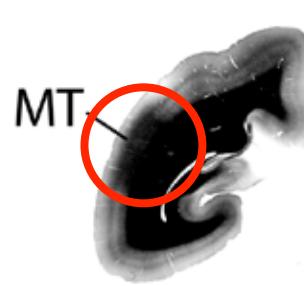
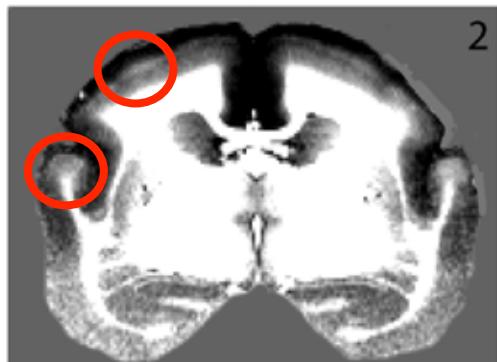
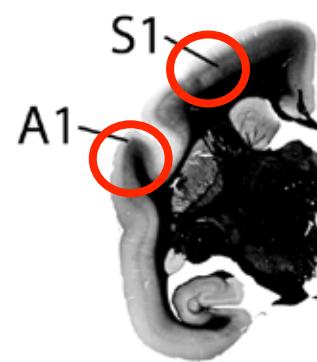
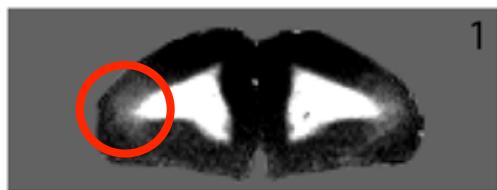


T_1 -Weighted MRI Reveals Cortical Myeloarchitecture

Myelin Stain



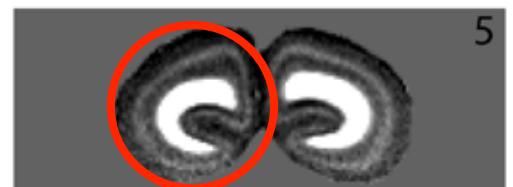
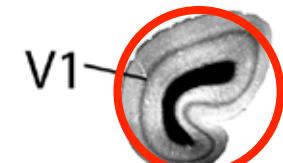
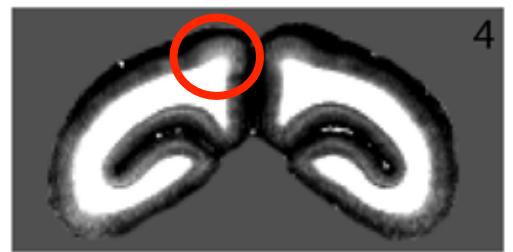
MRI



Myelin Stain



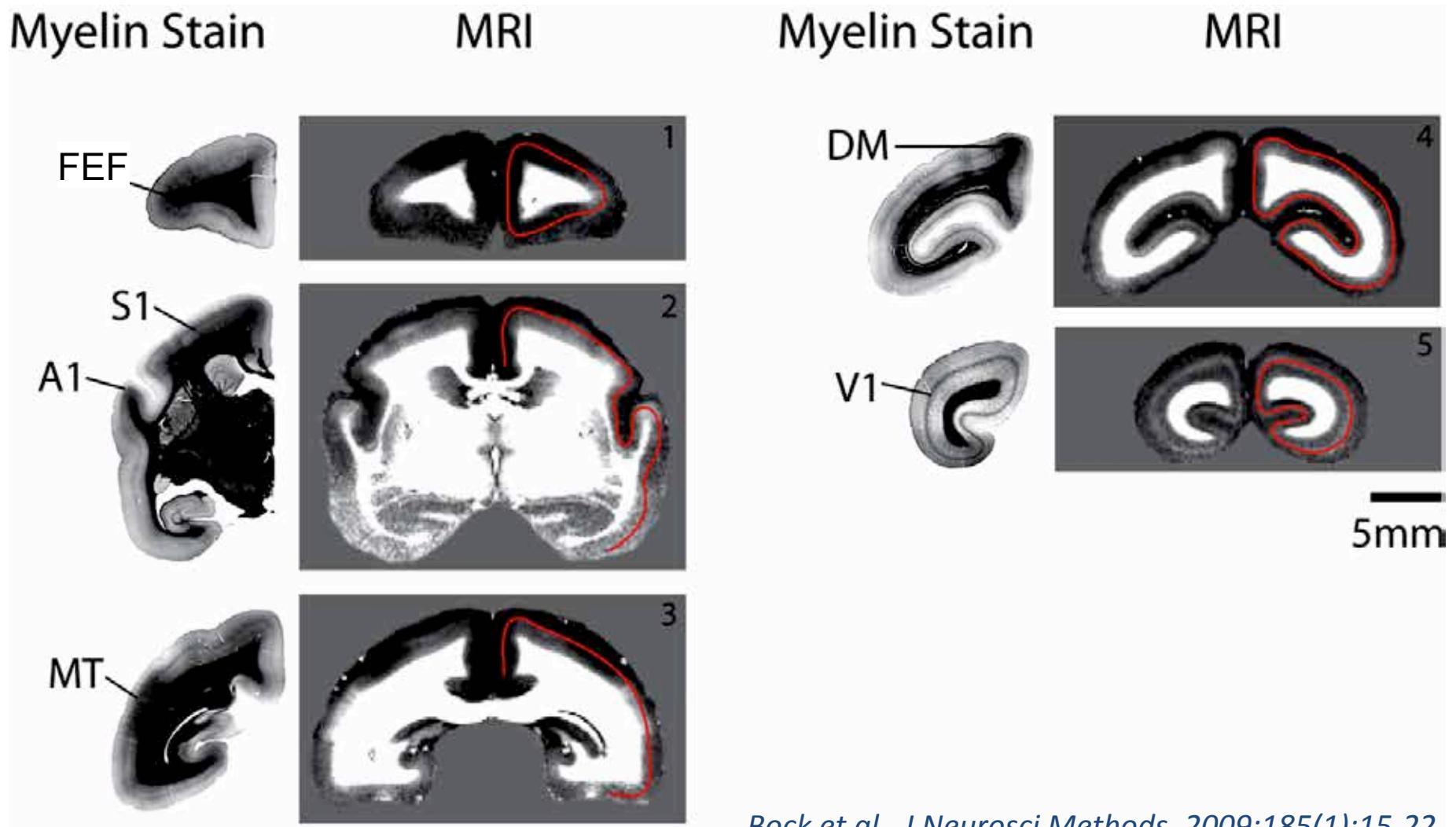
MRI



5mm

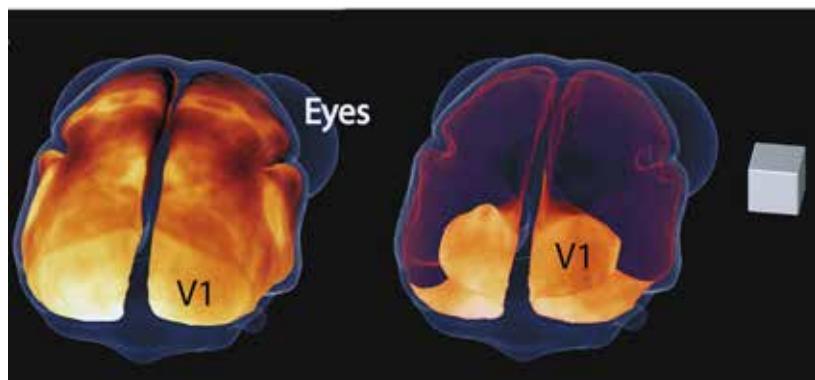
Bock et al., J Neurosci Methods. 2009;185(1):15-22

T₁-Weighted MRI Reveals Cortical Myeloarchitecture

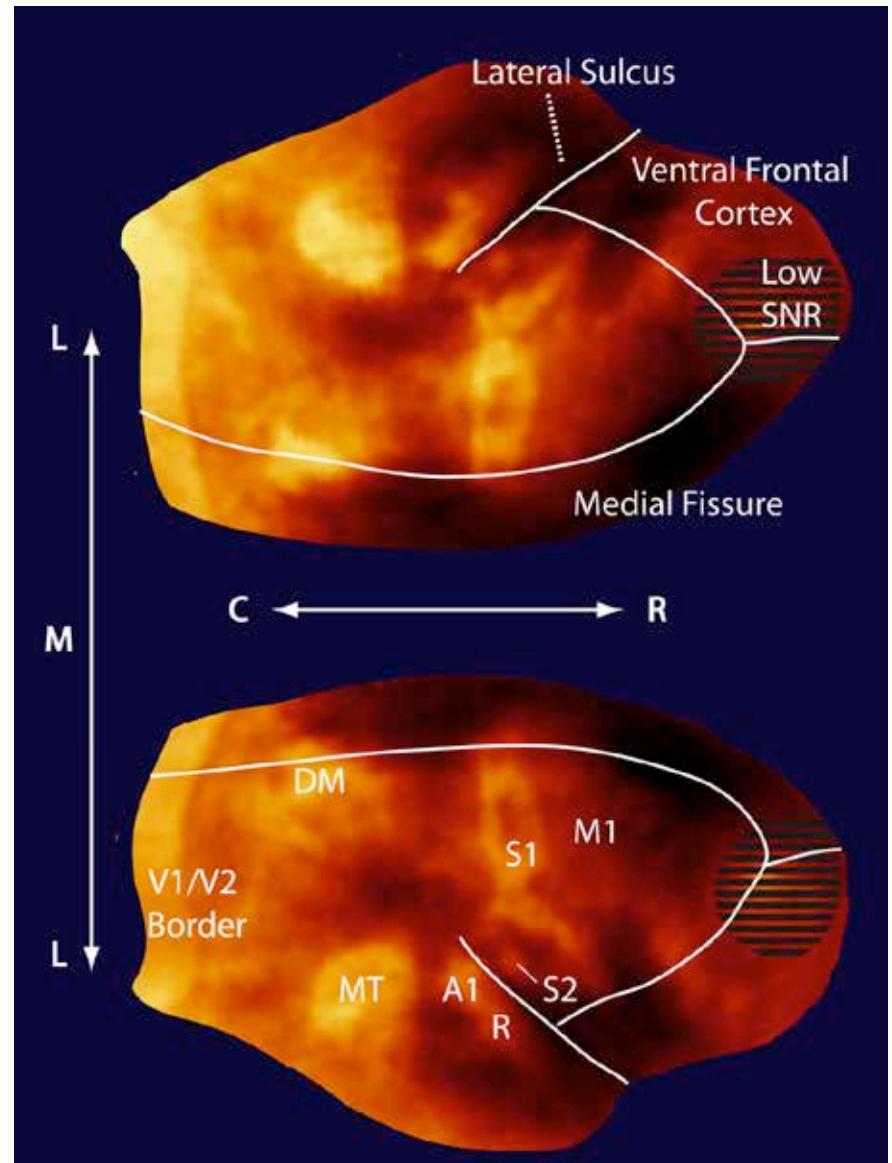


Bock et al., J Neurosci Methods. 2009;185(1):15-22

Cortical Myeloarchitecture Map

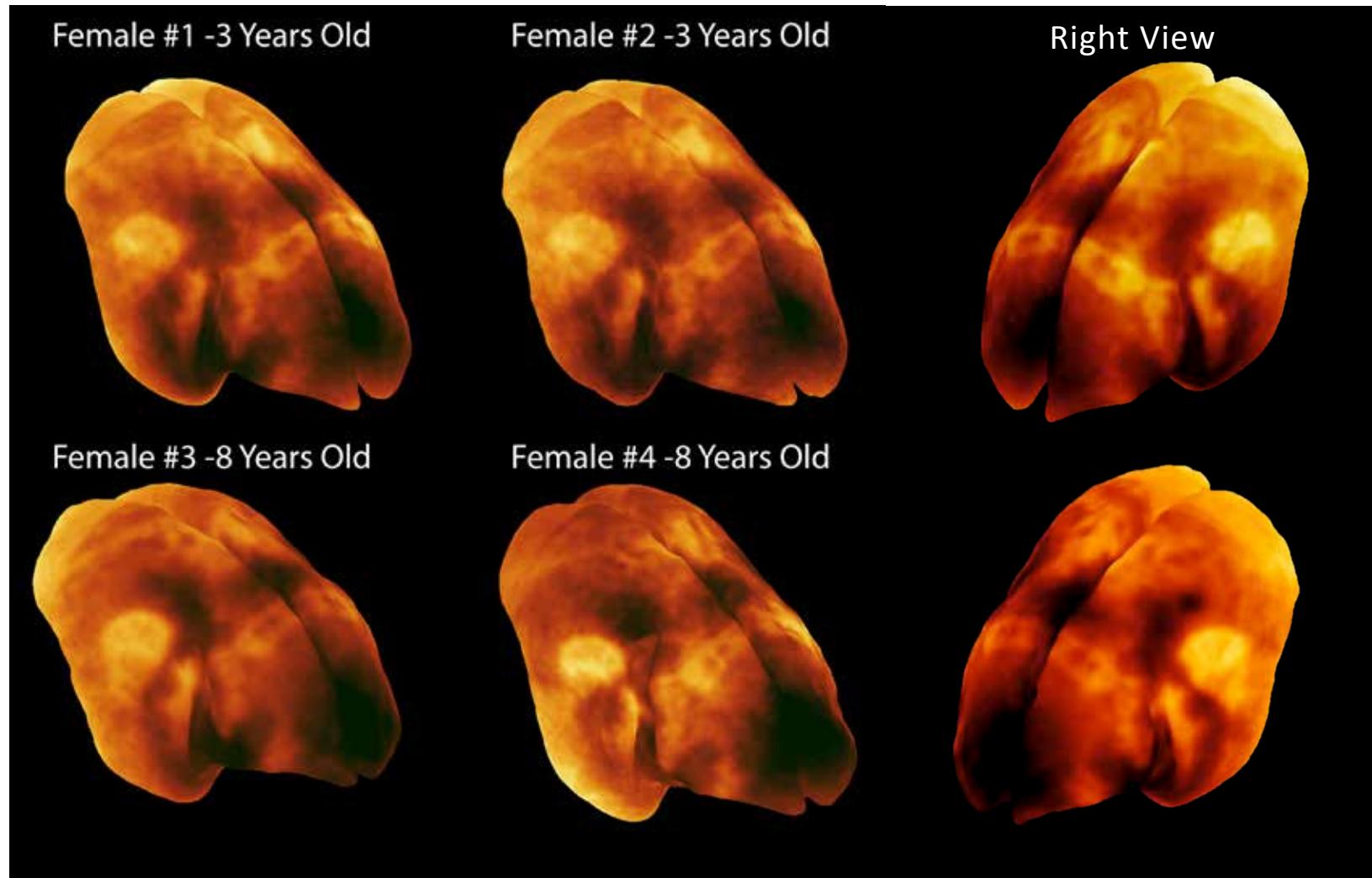


Voxel size $150 \mu\text{m}^3$

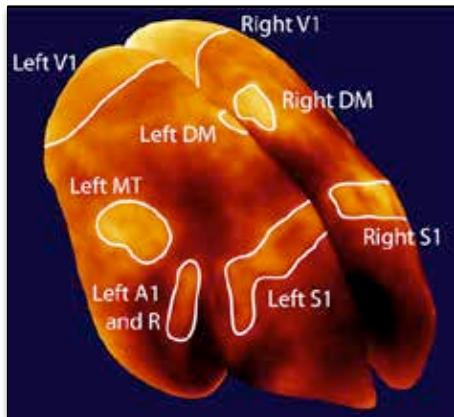


Bock et al., *J Neurosci Methods*. 2009 185(1):15-22

Reproducible and Quantitative Myeloarchitecture



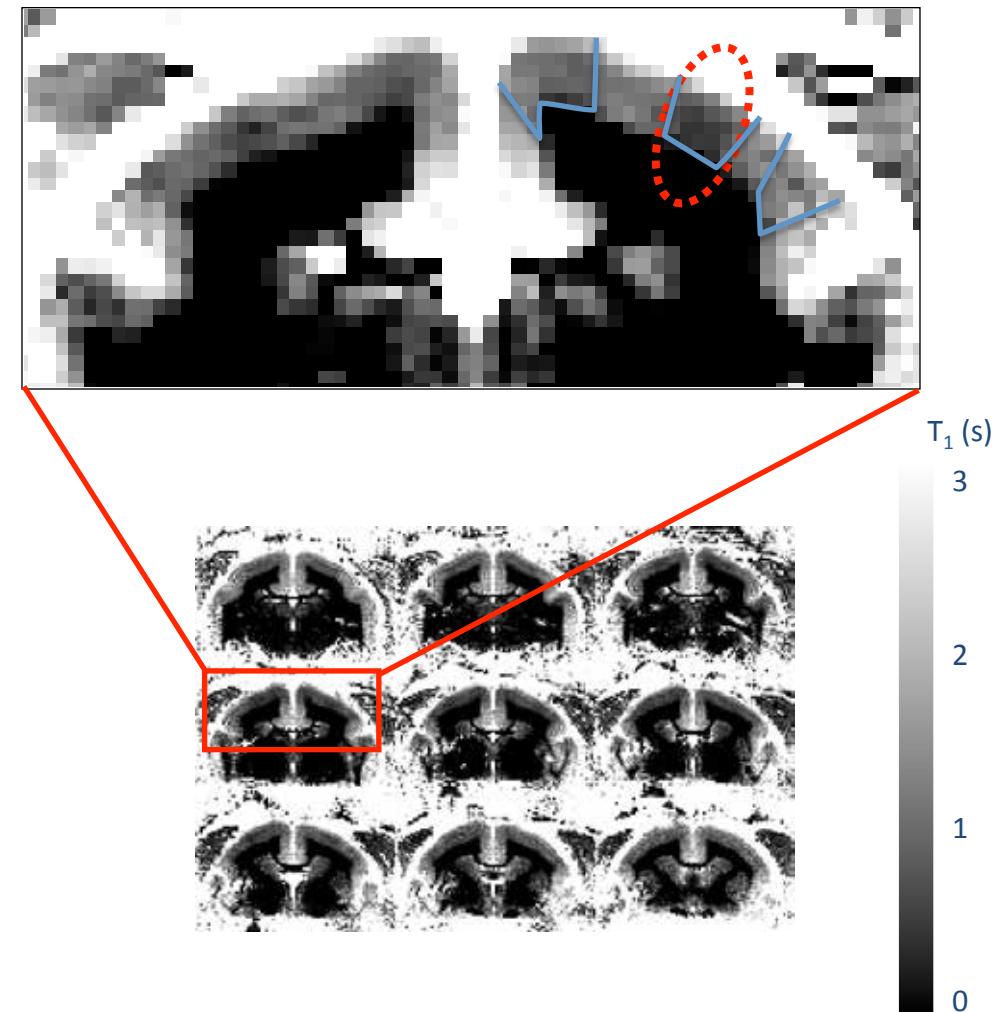
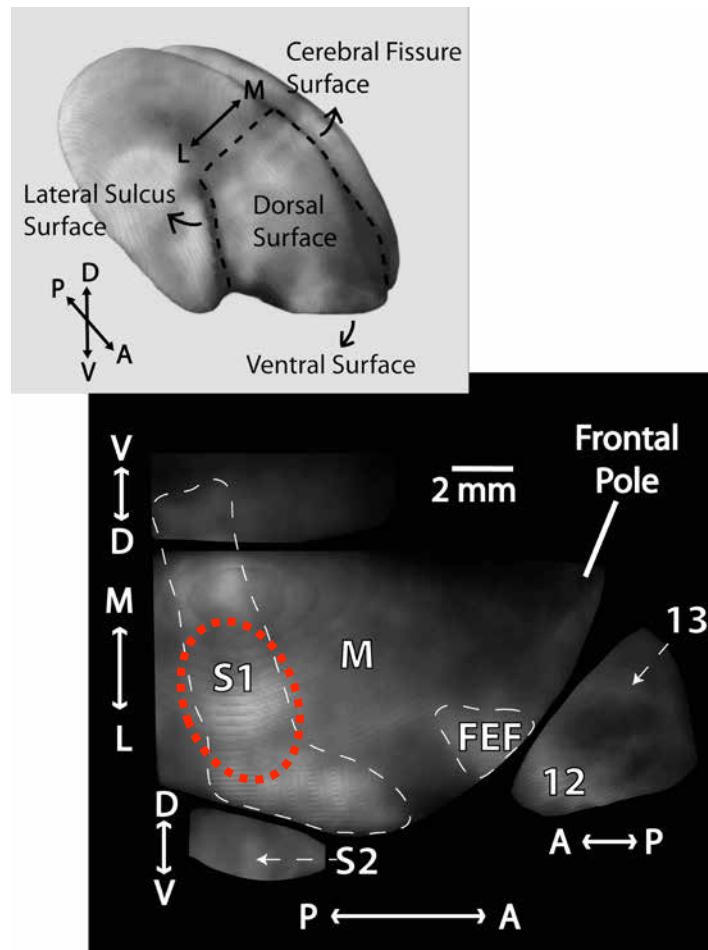
Reproducible and Quantitative Myeloarchitecture



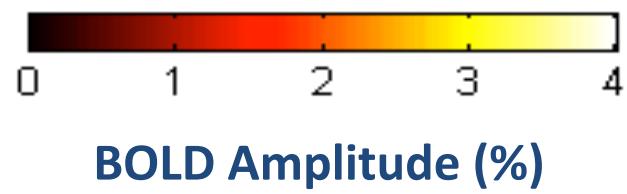
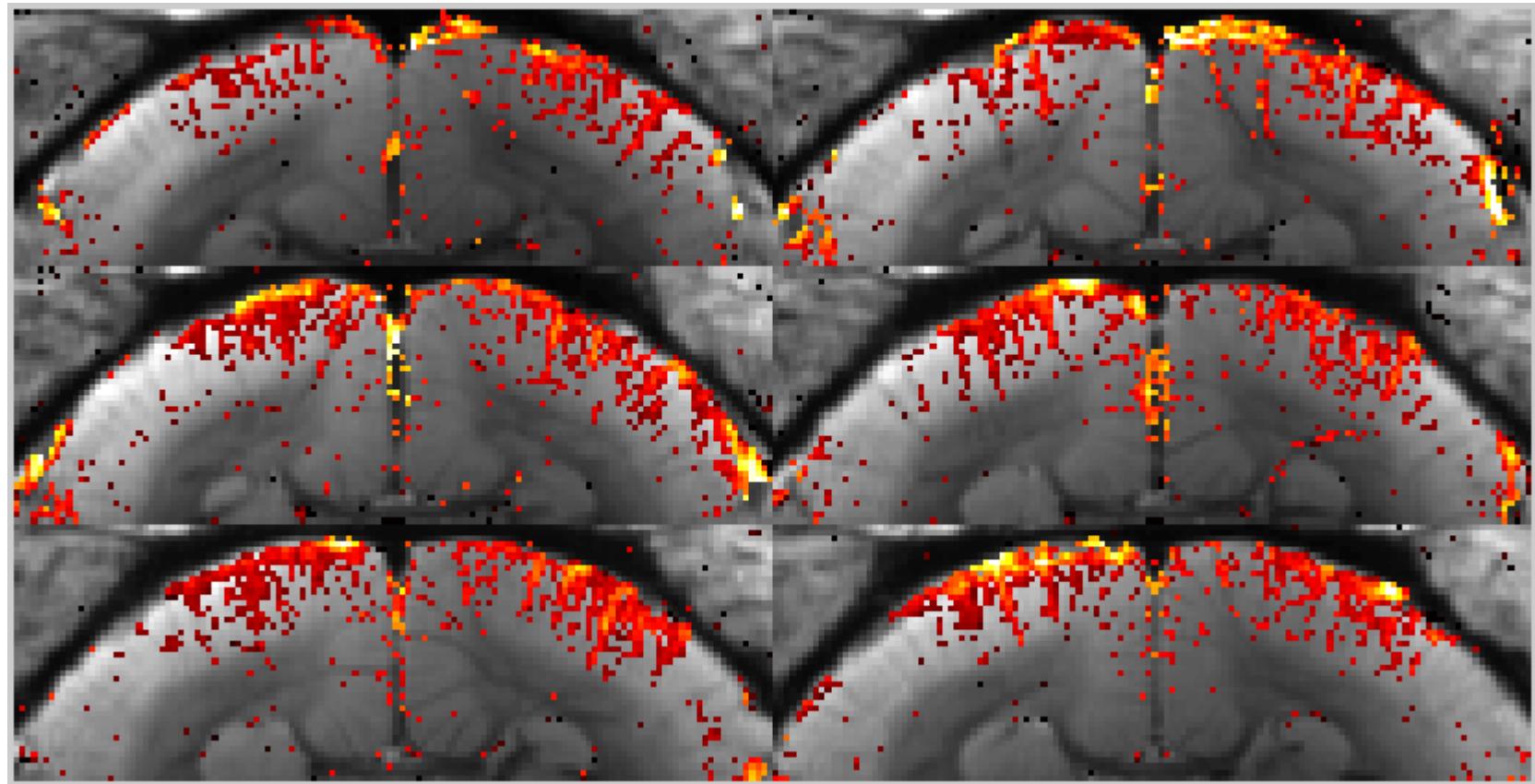
Region	Surface Area (mm ²)		Surface Area (%)
	Left	Right	
Cortex	1005 ± 21	1007 ± 34	100
V1	219 ± 12	222 ± 3	22
S1	28 ± 4	30 ± 4	3
MT	17 ± 3	19 ± 2	2
A1 and R	11 ± 3	11 ± 3	1
DM	8 ± 1	7 ± 1	1

- Agrees well with histological measures of areas:
 - V1: 200-205 mm²: *Fritsches and Rosa 1996 JCN 372:264-82; Missler, Wolff 1993 JCN 333:53-67*
 - MT: 14 mm²: *Pessoa et al. 1992 Exp. Brain Res. 2: 459–462.*
 - DM: *no well defined borders.*
- More than $\frac{1}{4}$ of the marmoset cortex dedicated to processing of visual information

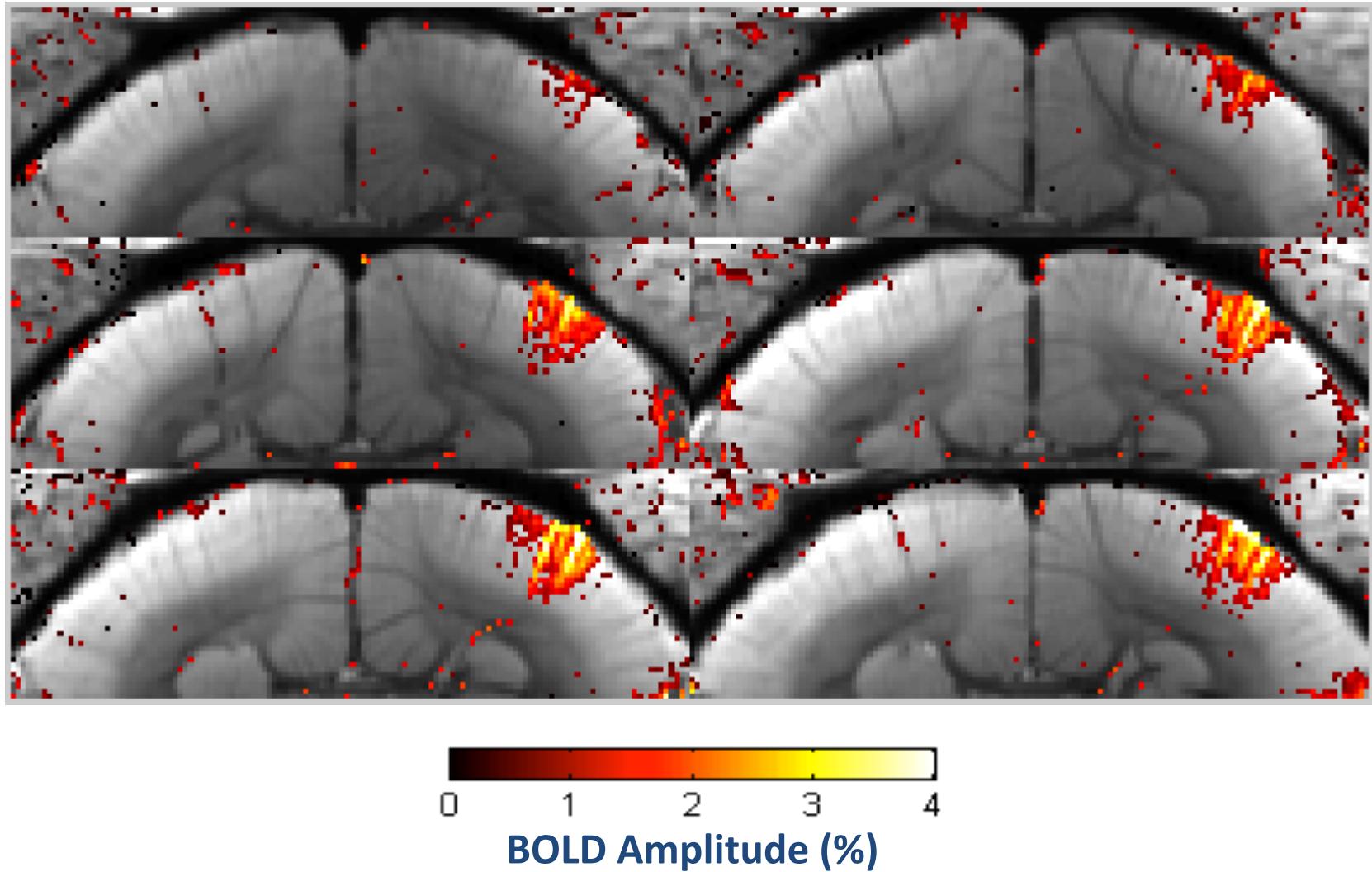
T_1 Mapping of Primary Somatosensory Cortex



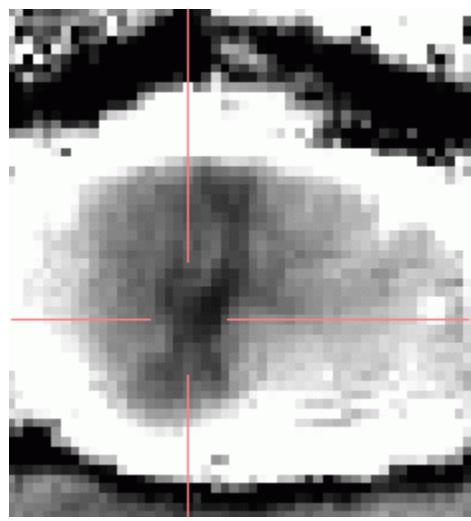
Transient Response, Short-duration Stimulus



Sustained Response, Long-duration Stimulus

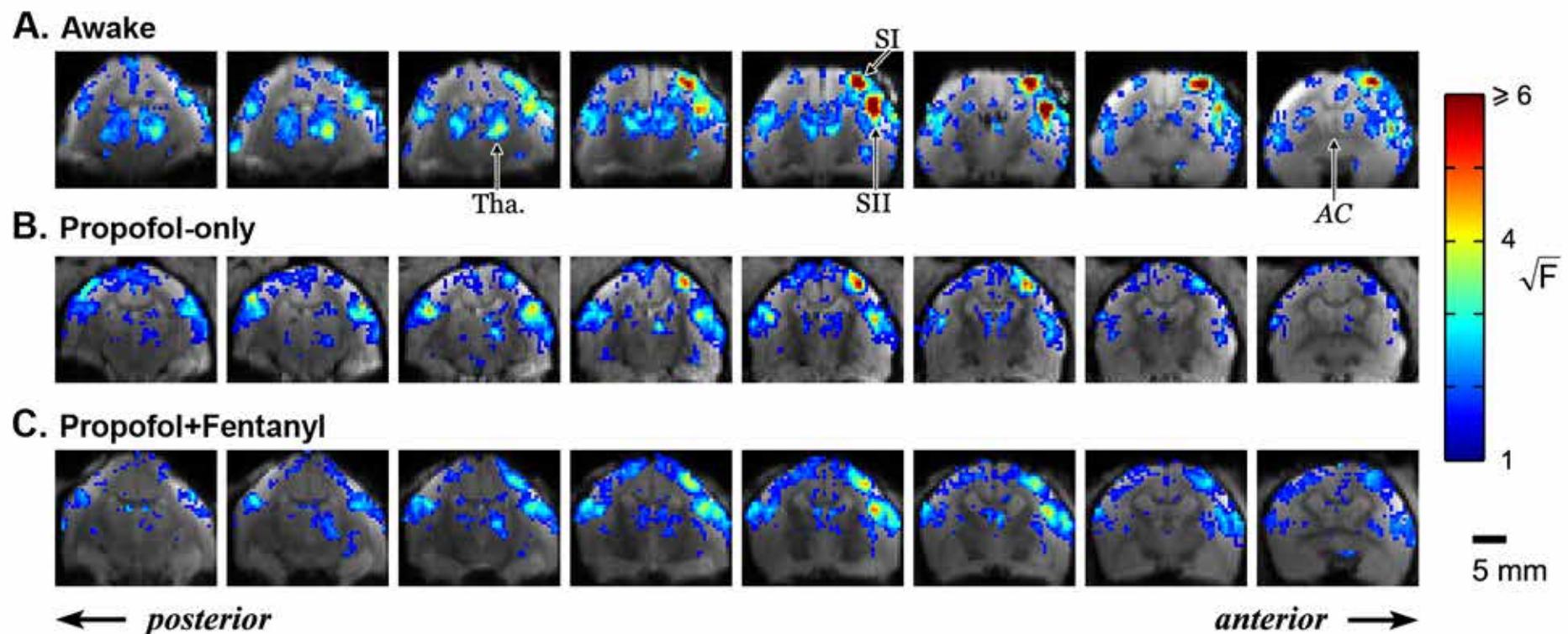
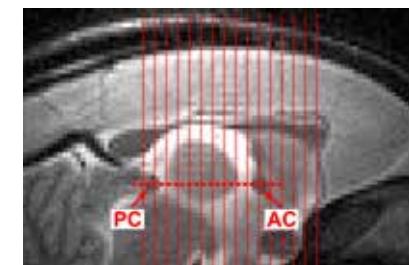


Localization of Sustained Response on T_1 map

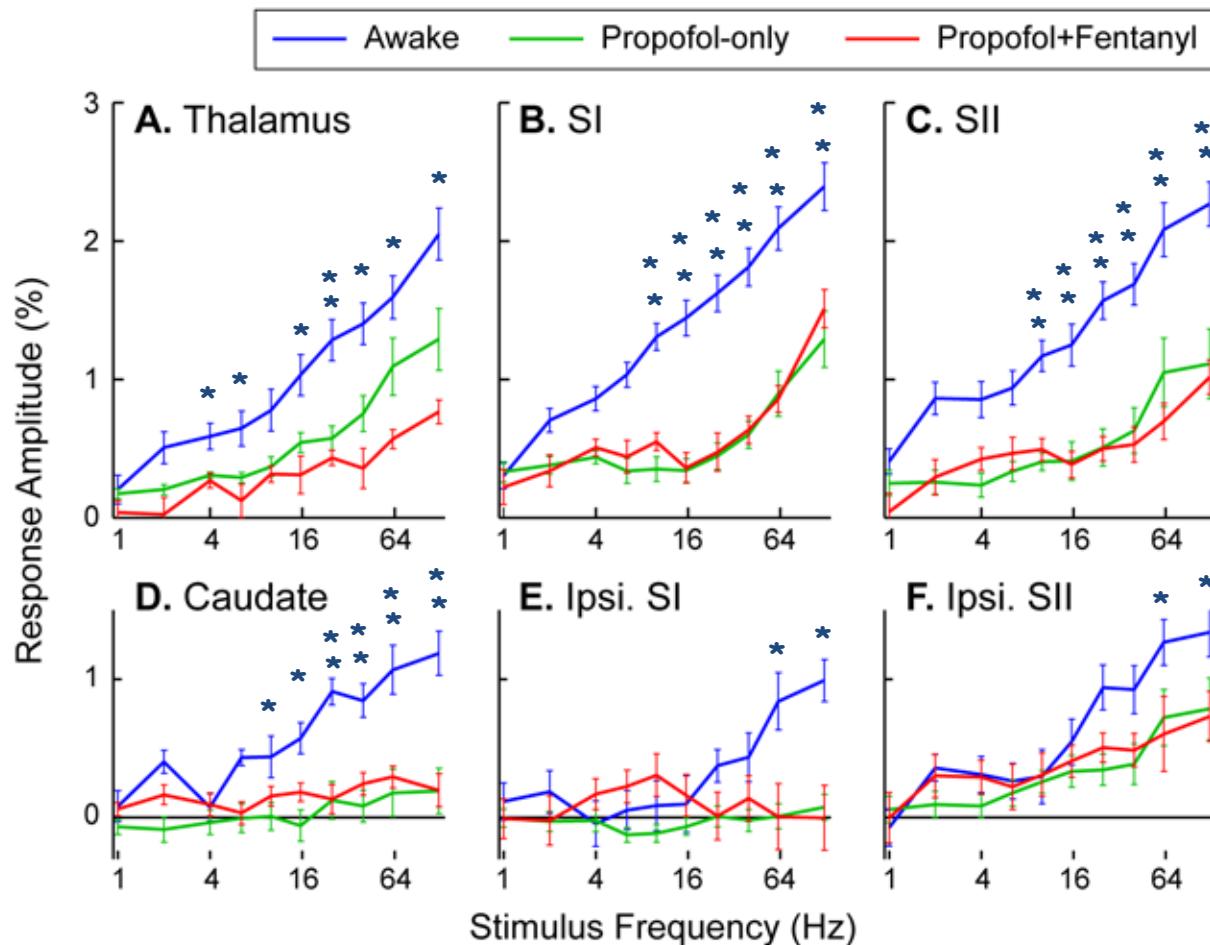


The Influence of Anesthesia: More Widespread Spatial Extent of Functional Regions in Awake Marmosets

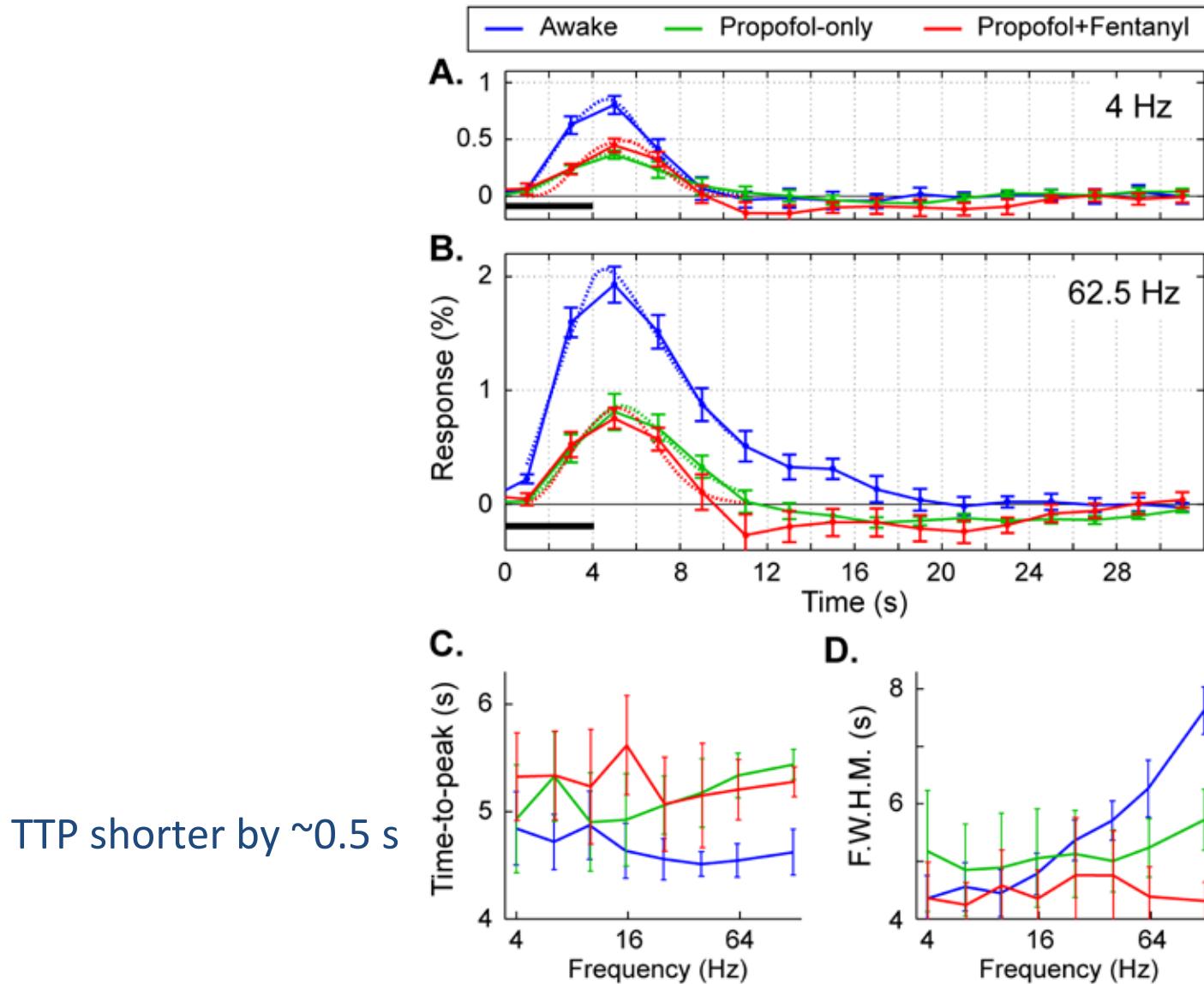
Responses throughout the somatosensory pathway significantly enhanced when compared to anesthetized subjects



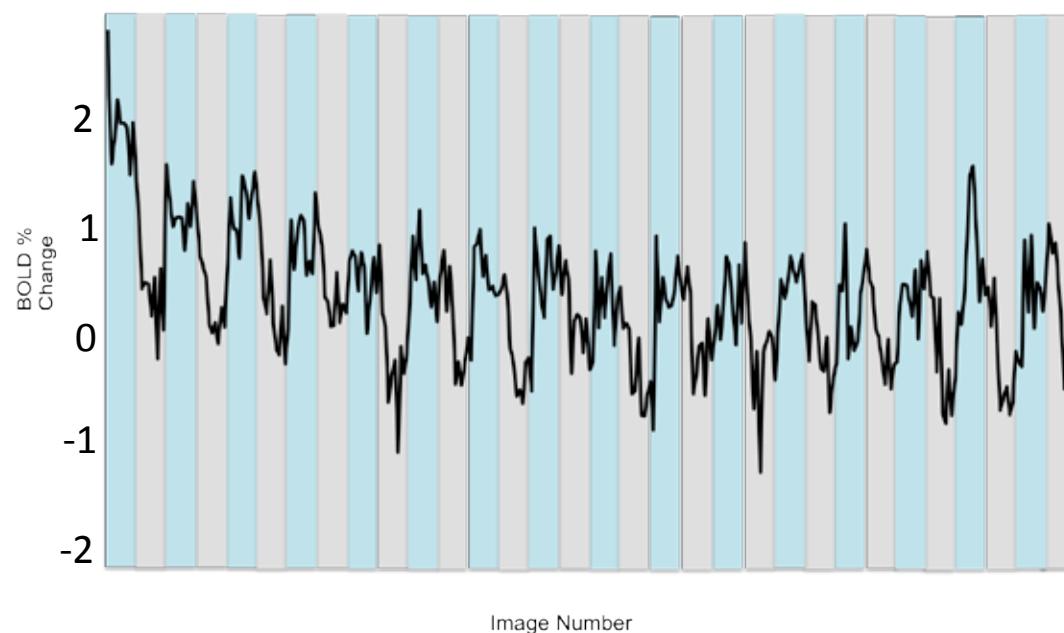
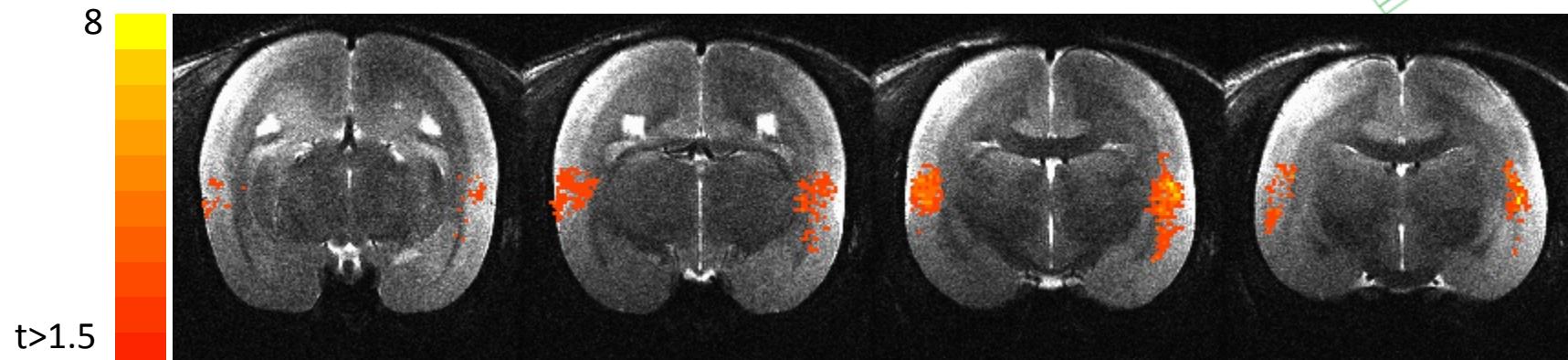
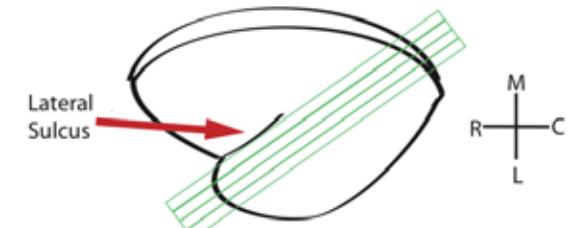
Amplitude of BOLD HRF Significantly Enhanced at High Stimulus Frequencies in Awake Monkeys



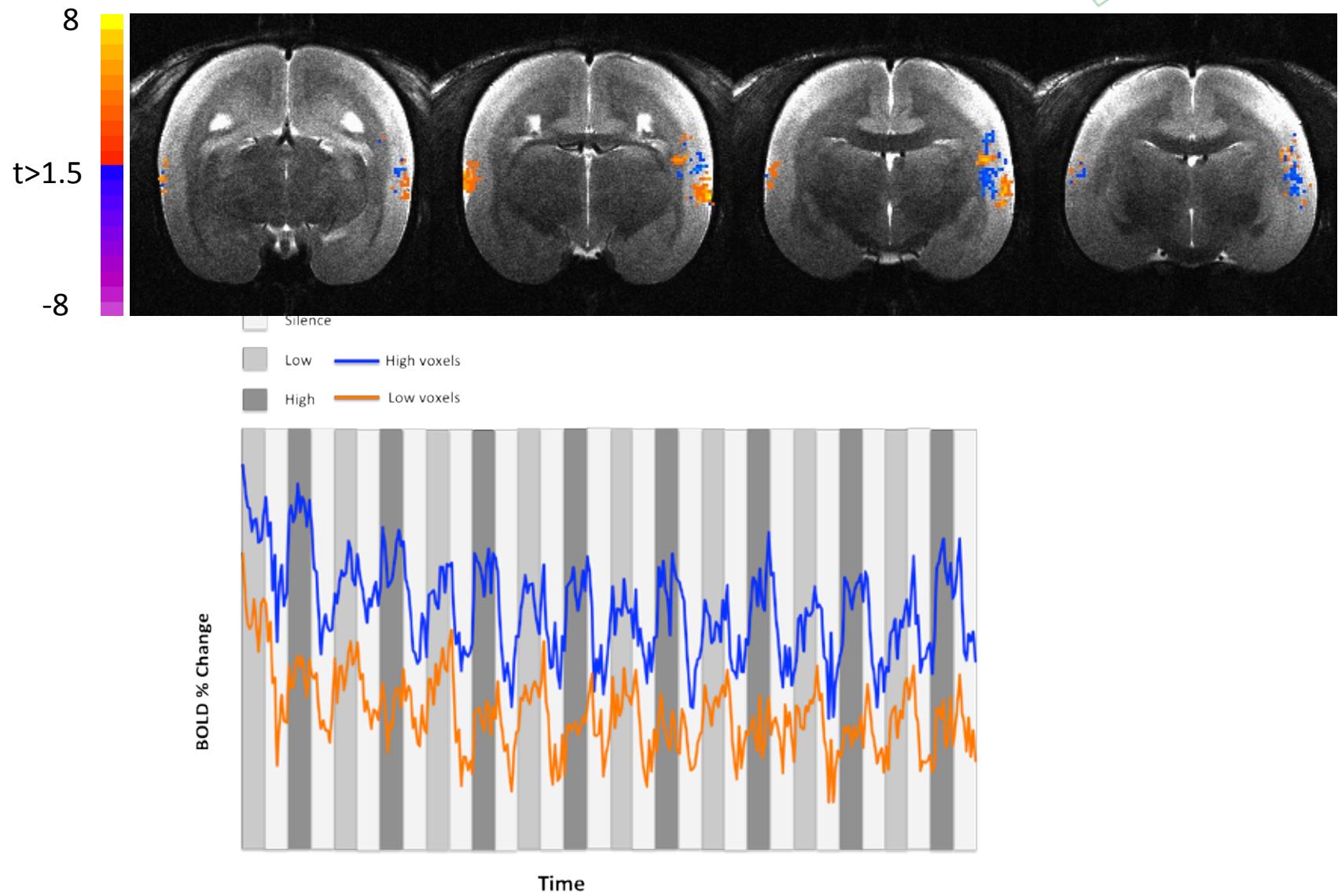
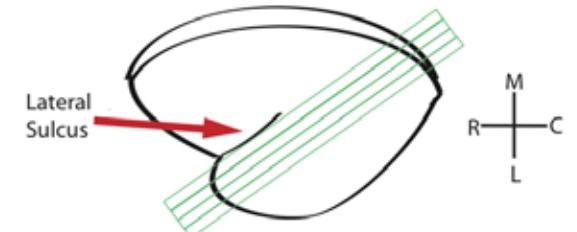
BOLD HRF in Awake Marmosets Has Faster Times-to-Peak



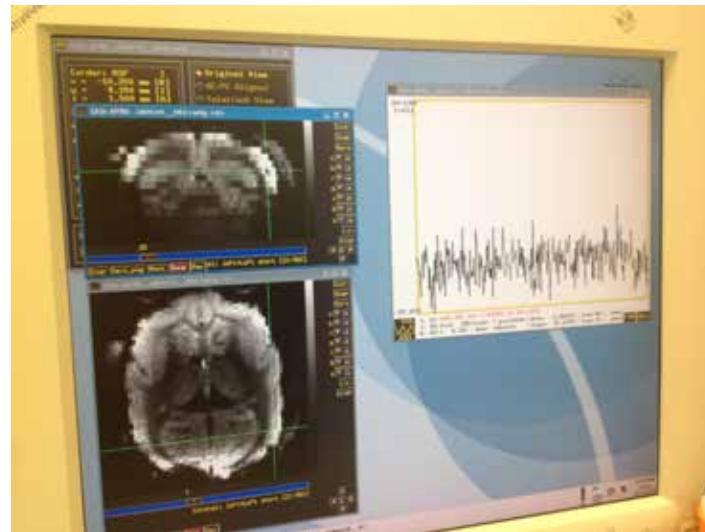
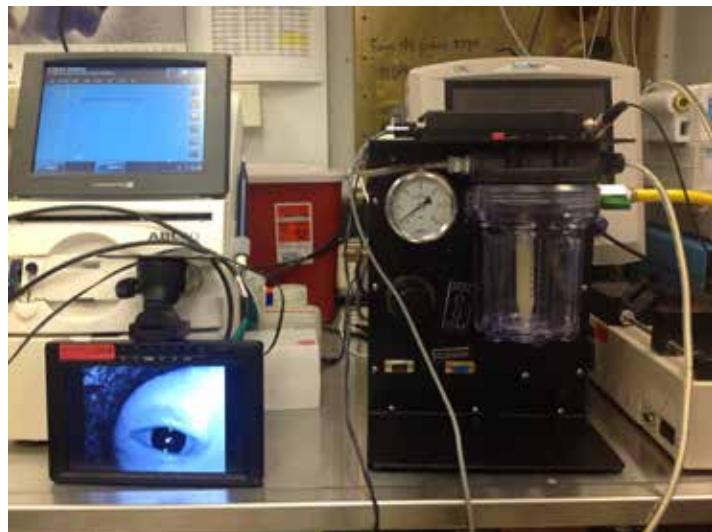
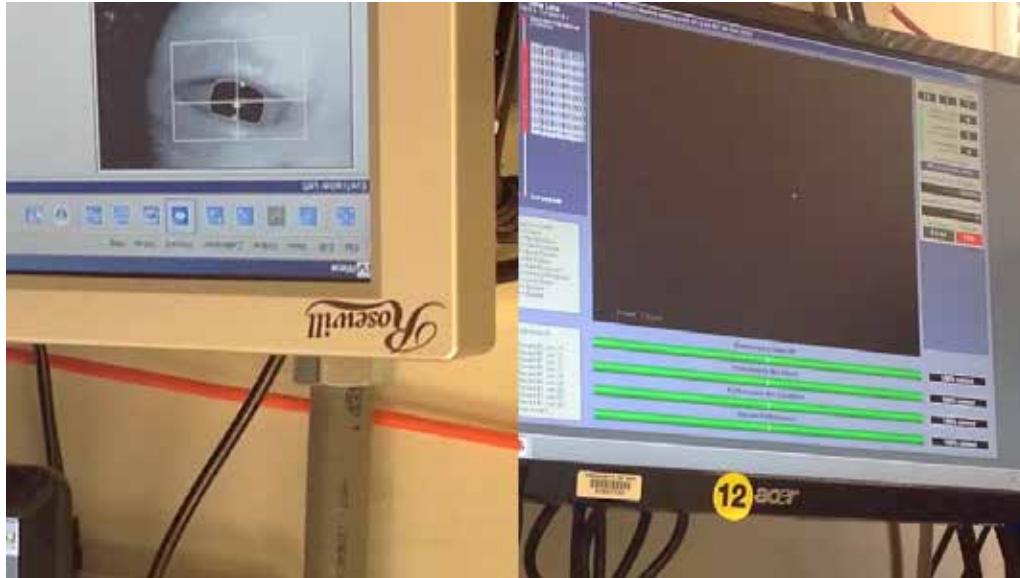
Auditory fMRI in Awake Marmoset



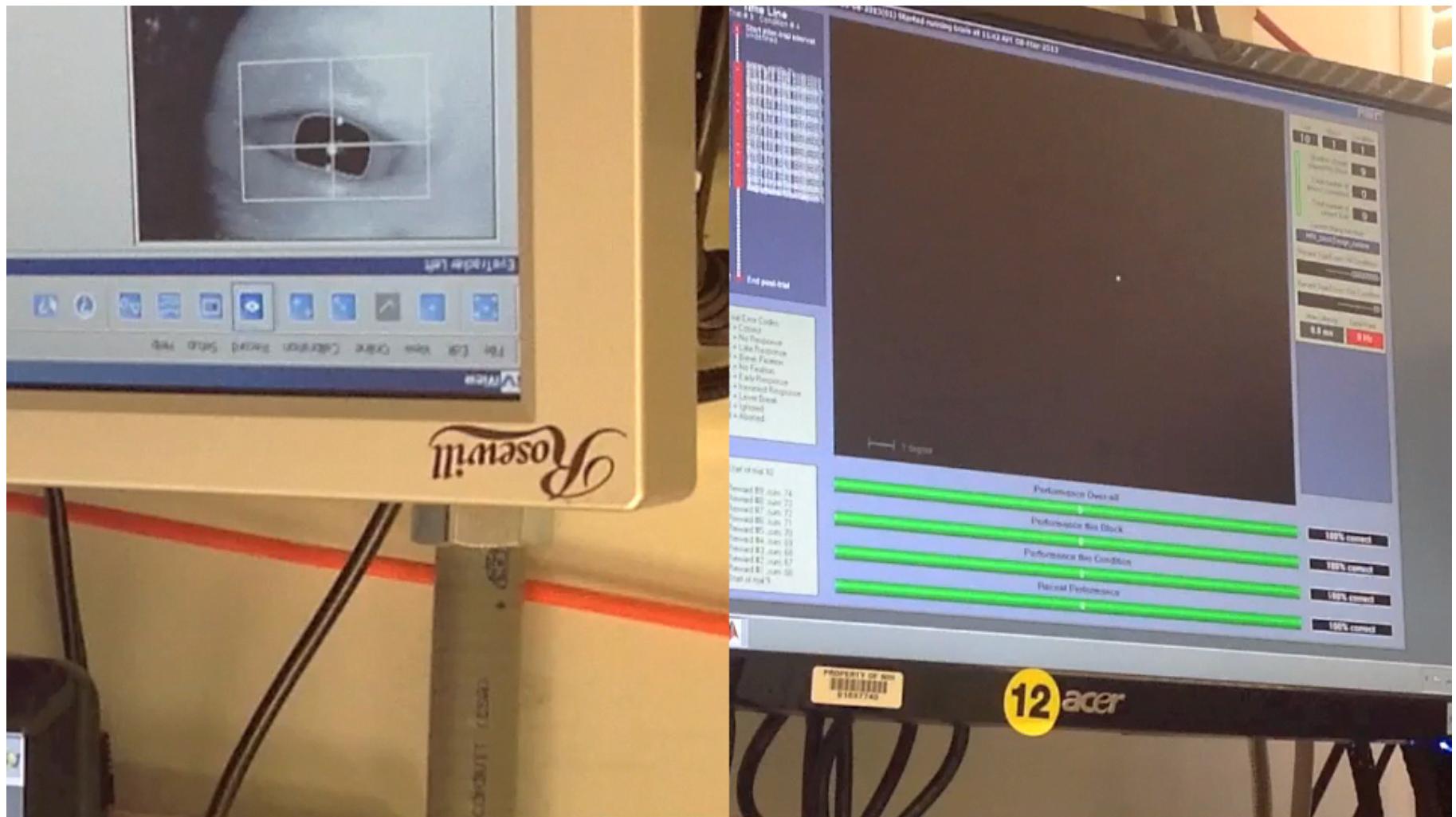
Auditory fMRI in Awake Marmoset



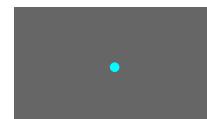
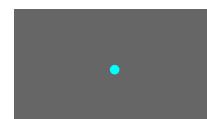
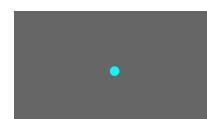
Visual fMRI in Awake Marmoset: Setup



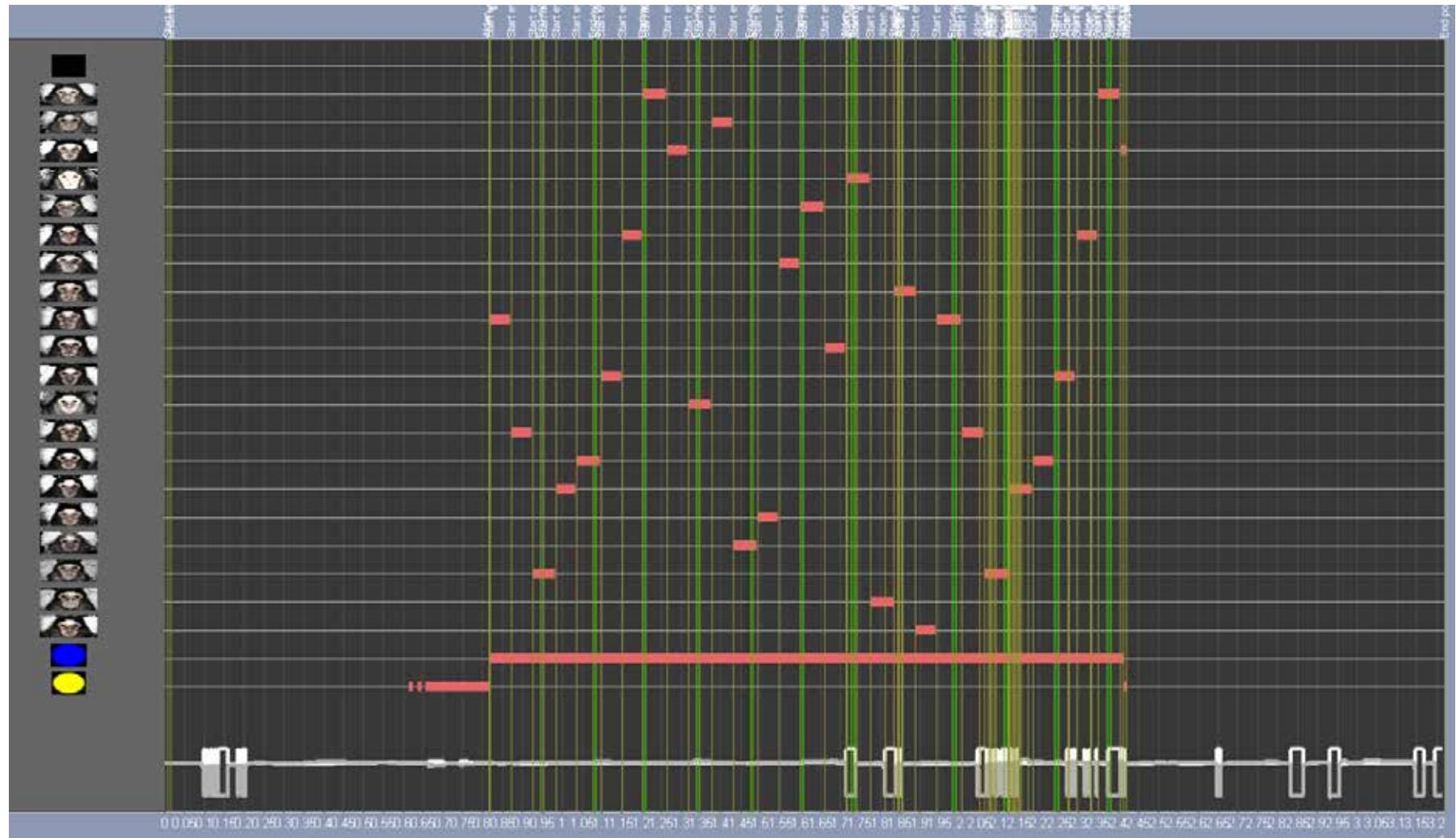
An example block



Stimuli Categories

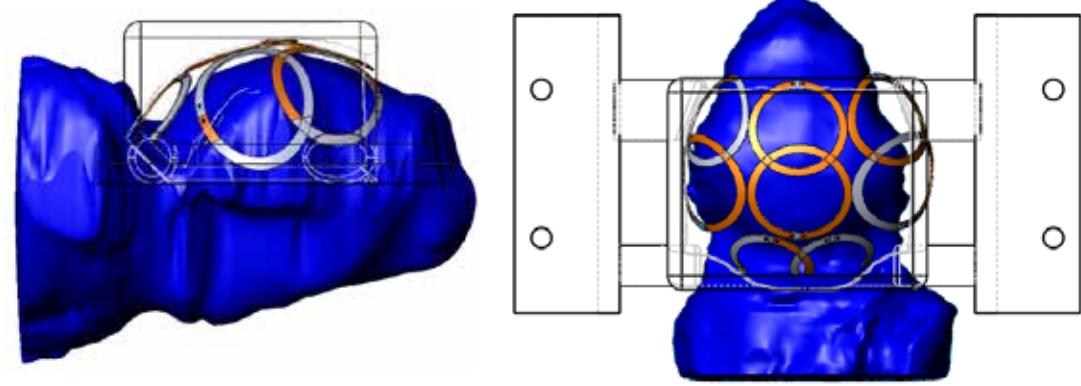
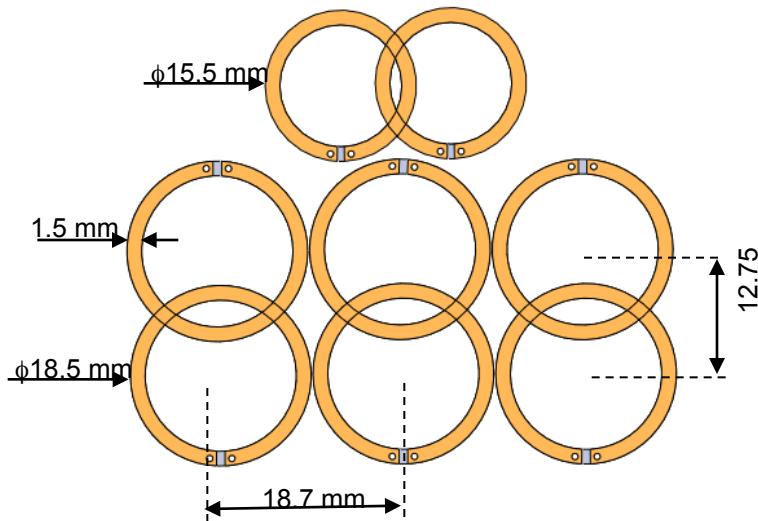
	Body Parts	Objects	Scenes	Spectral scrambled	Spatial scrambled	Fixation Point	
Faces							
							
							
							
							
							

A trial in the scanner



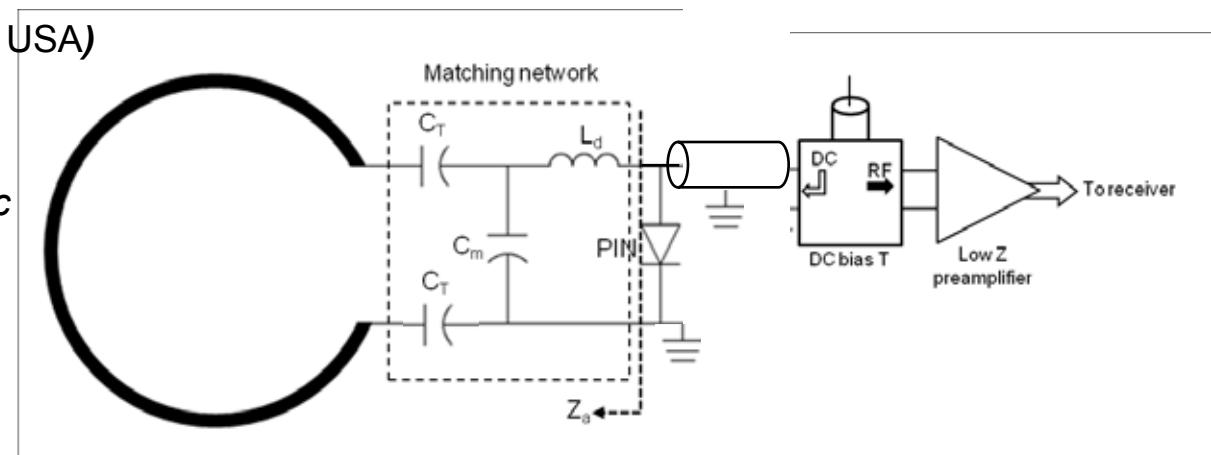
8 – Channel embedded array for visual fMRI - ELI

Eli's Coil layout



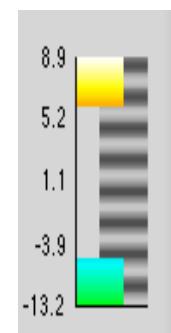
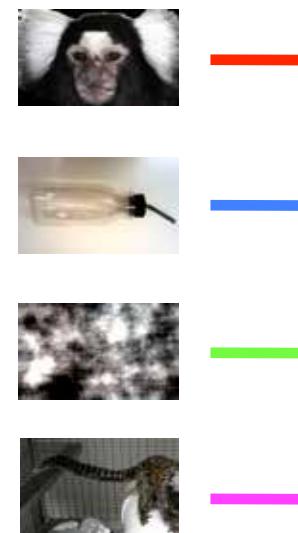
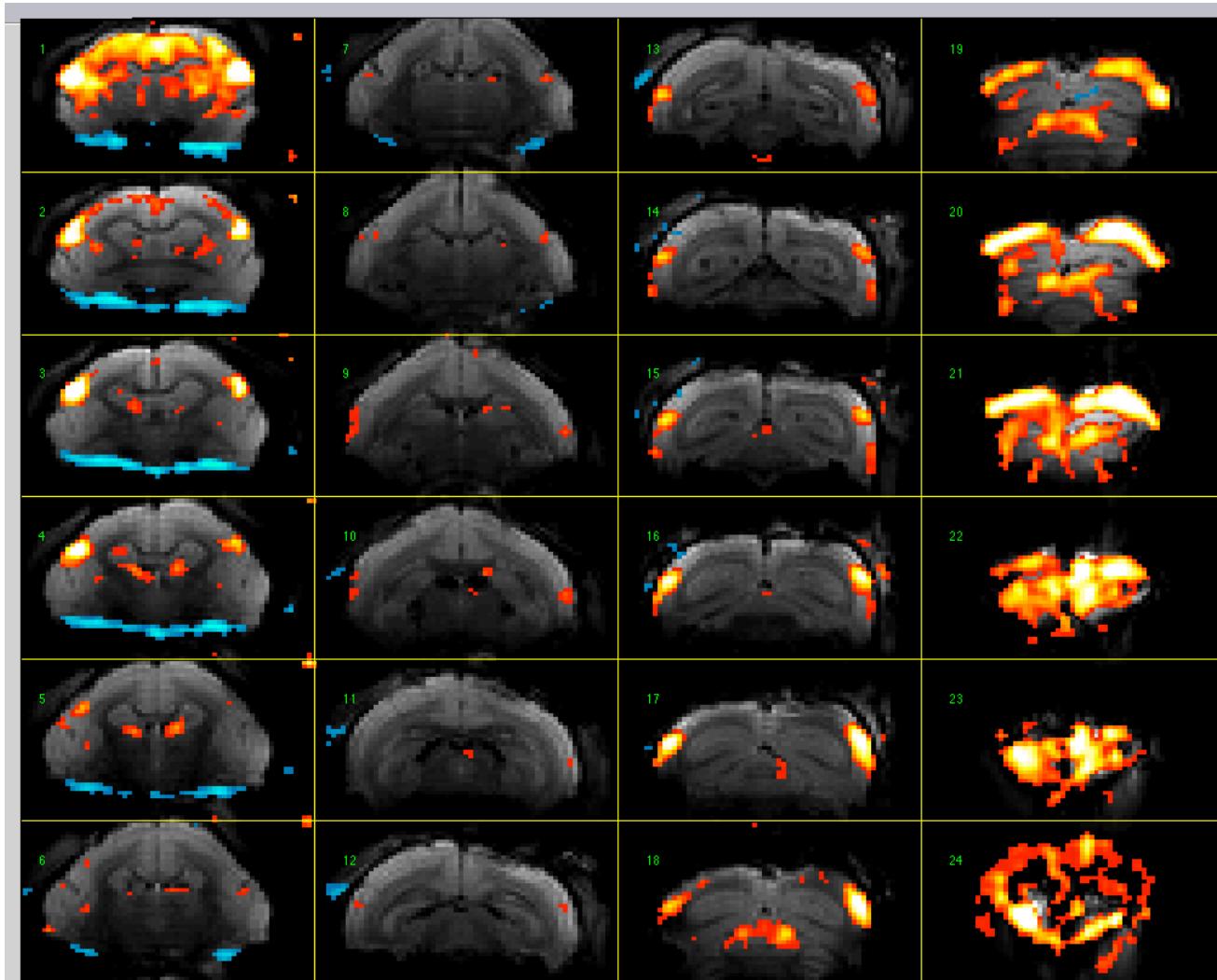
CuFlon (Polyflon Inc., Norwalk, CT, USA)

- 2oz/ft² of copper deposited
- 0.25 mm thick PTFE dielectric



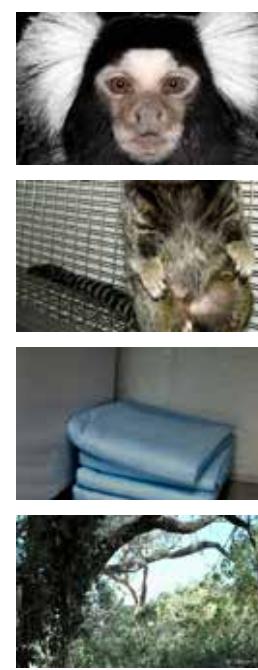
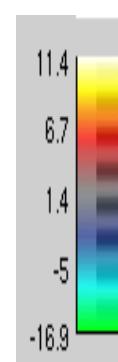
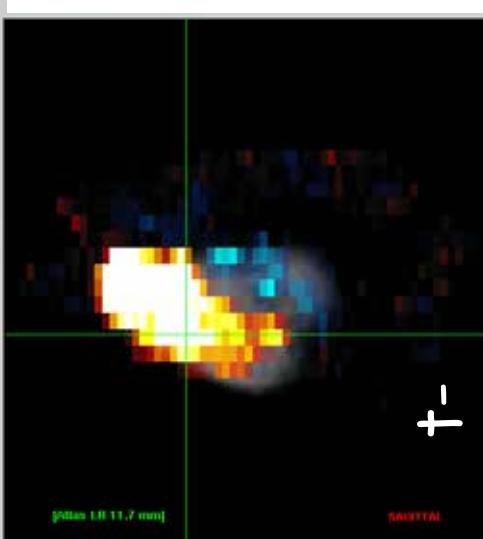
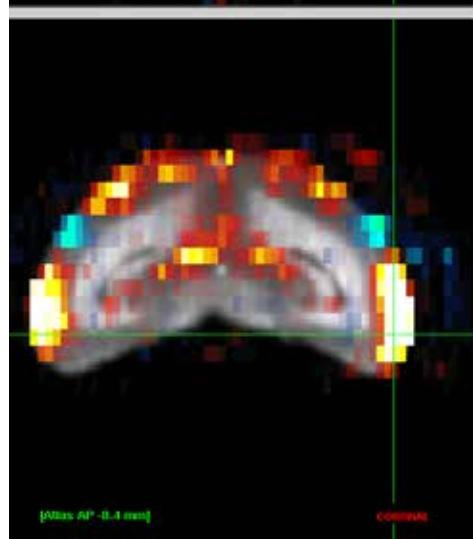
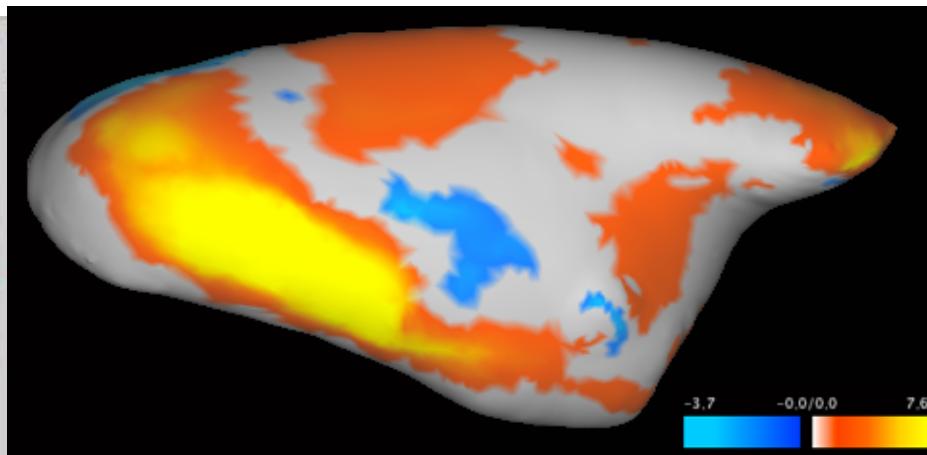
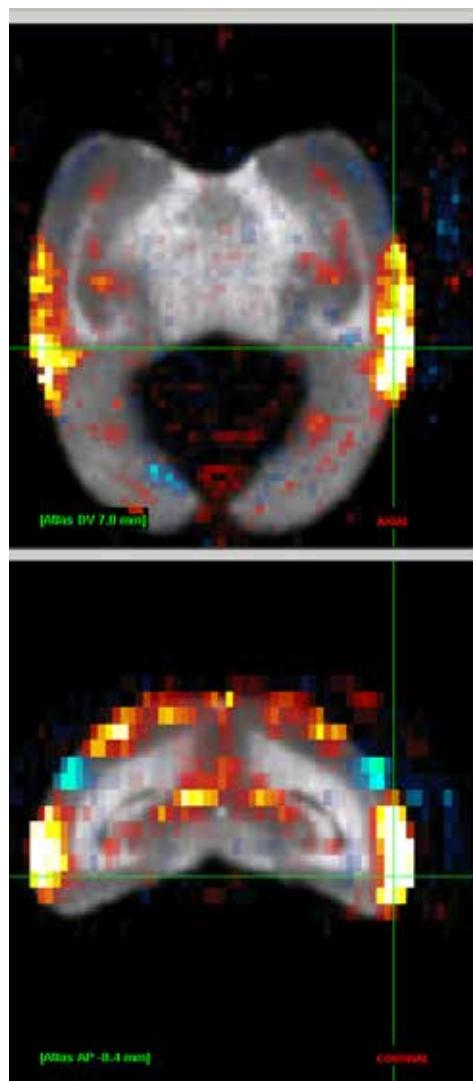
Single element electric

Visual Stimuli vs. Rest



t-value

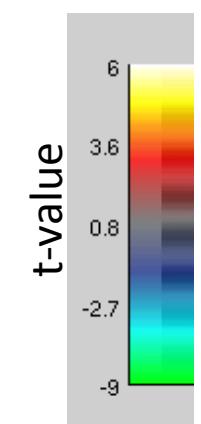
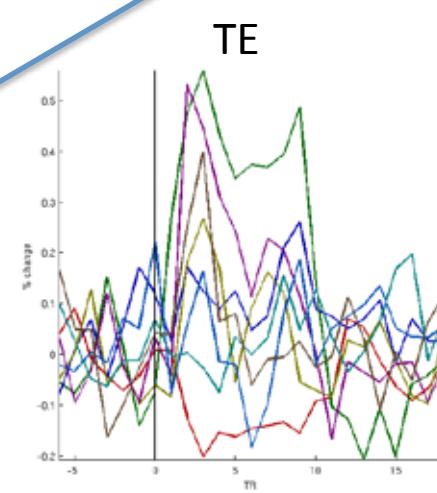
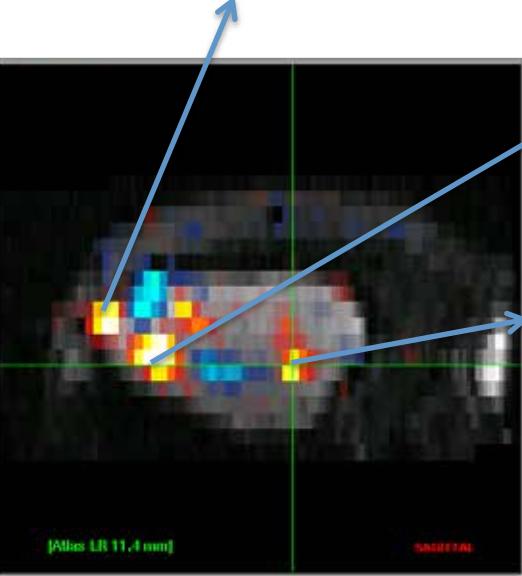
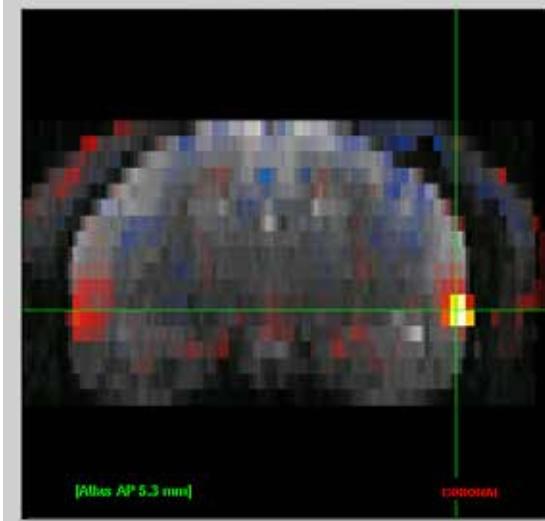
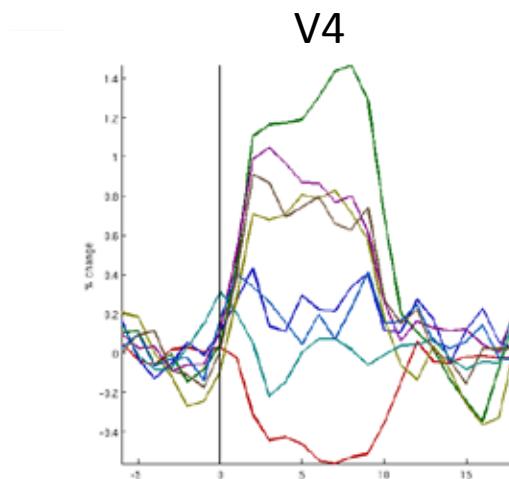
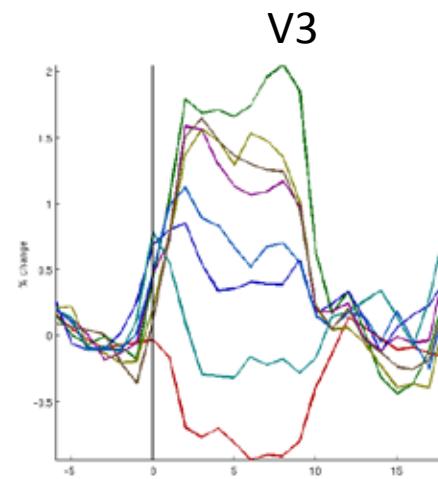
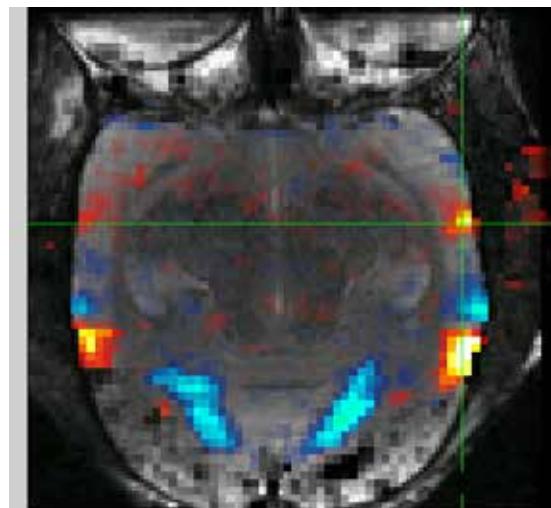
Visual fMRI: Intact versus scrambled



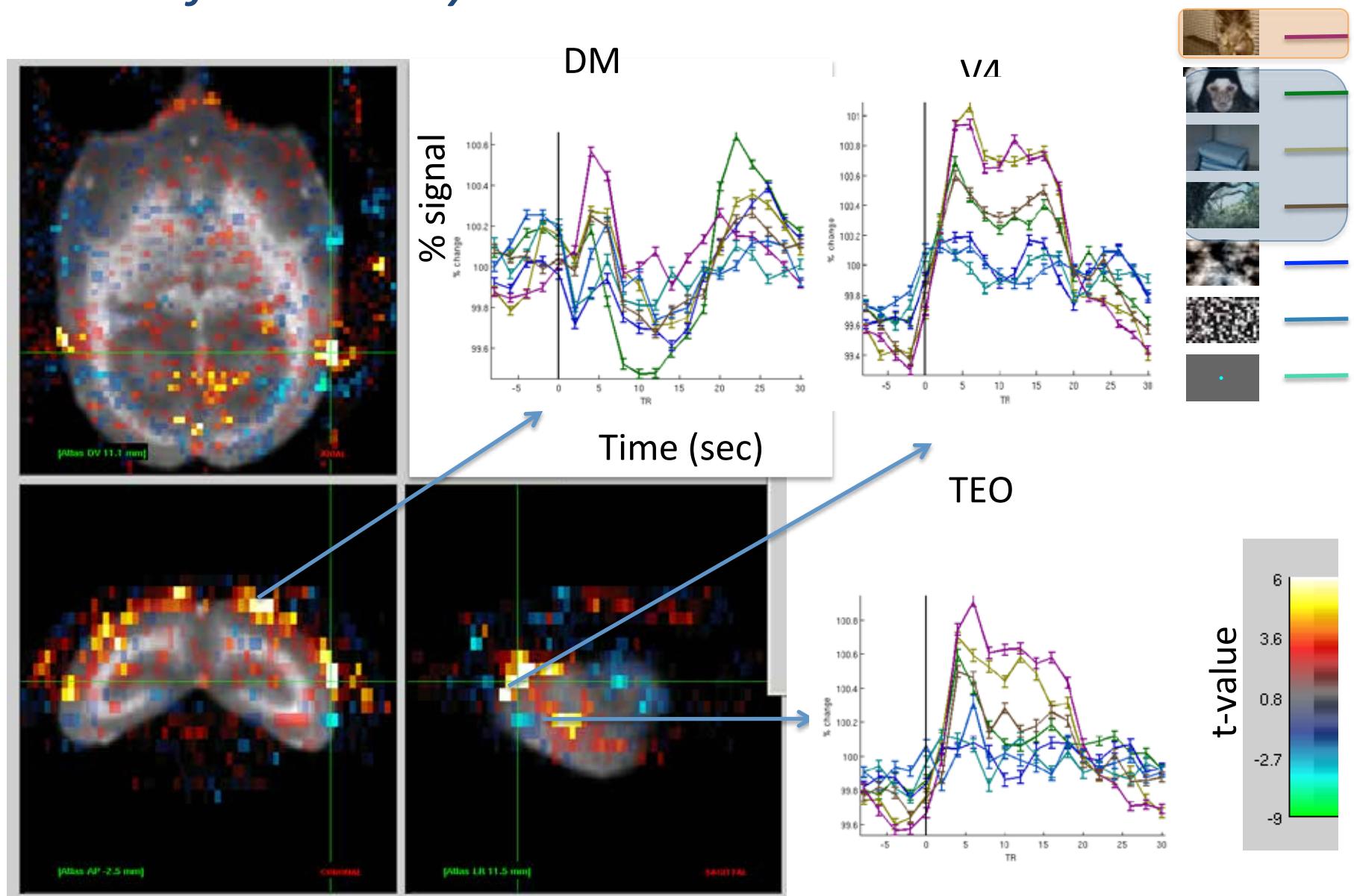
VS.



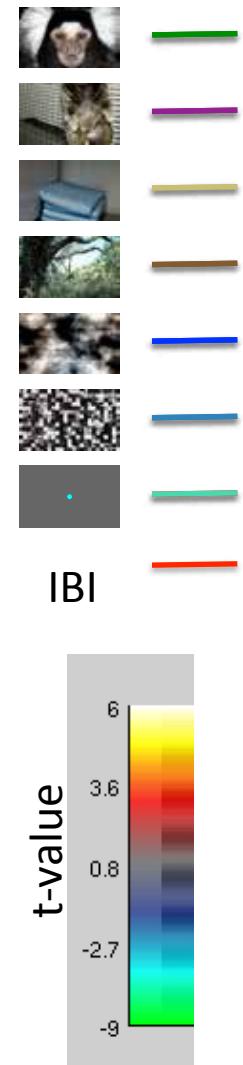
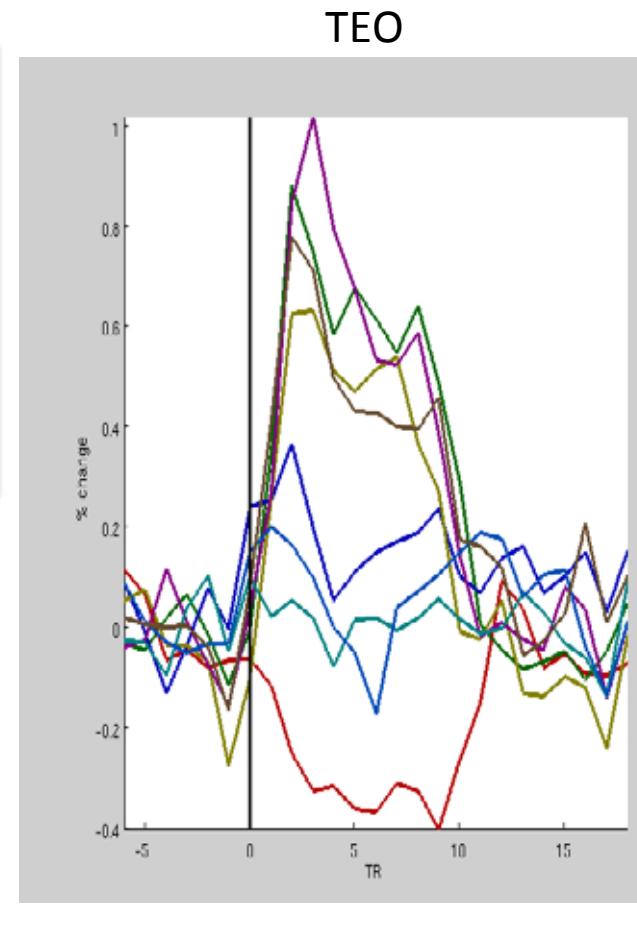
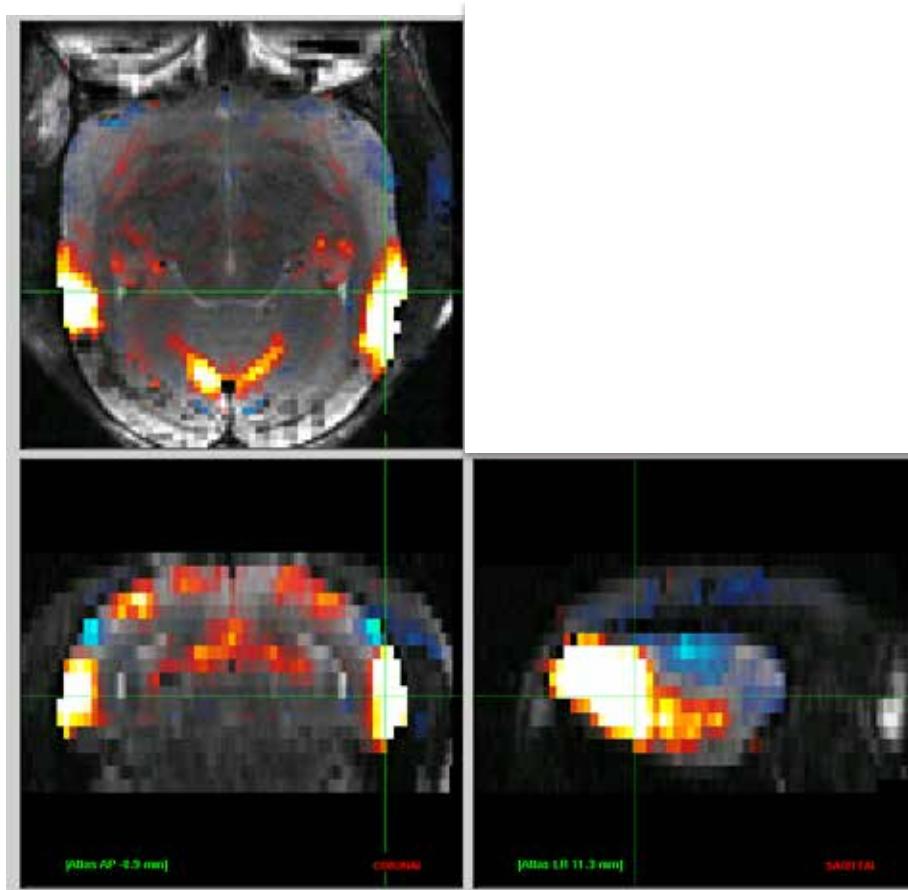
Visual fMRI: Face Selective Areas



Visual fMRI: Body selective areas



Visual fMRI: Object Recognition Pathway



Conclusions

- Advantages of Animal Models
 - Allow comprehensive, multi-modal investigations
 - Can be Performed in State of the Art MRI Systems
 - High SNR, Spatial and Temporal Resolution
- Challenges
 - Use of *anesthesia* is a major confound for fMRI studies
 - Training of animals to perform specialized tasks can be quite challenging



Thank You!